Docket No.: 1718-0214P
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent of:
Harmenberg, Johan et al.

U.S. Patent No.: RE39,264 E

Issued: September 5, 2006

For: Pharmaceutical Combination

CORRECTED REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Mail Stop: Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA
22313-1450

September 28, 2009

10/01/2009 RMEBRAHT 00000053 022448 RE39264
01 FC:1457 1120.00 DA

Sir:

This corrected Request for Extension of Patent Term Under 35 U.S.C. § 156 is being timely filed via Express mail on the above date. A Request for Extension of Patent Term Under 35 U.S.C. § 156 was also timely filed on Friday, September 25, 2009 via EFS Web. The instant filing reflects some amendments made to the original Request and should be used as the basis for review.

Pursuant to 35 U.S.C. §165 and 37 C.F.R. §§1.710-1.791, Medivir AB of Huddinge, Sweden (hereinafter "Applicants"), hereby request an extension of the patent term due to regulatory review for U.S. Patent No. RE39,264 E, which was granted on September 5, 2006 from a reissue application based on US patent 6,337,324. Applicants represent that they are the owners and assignees of the entire interest in and to United States Patent No. RE39,264 (Exhibit 1, hereinafter "the '264 patent") by virtue of an assignment from the inventors Johan Harmenberg and Ann Harriet Margareta Kristofferson that was recorded in the parent patent (US

6,337,324) from which instant patent reissued, according to the following chain of events: assignment from Johan Harmenberg and Ann Harriet Margareta Kristofferson to Astra Aktiebolag, recorded March 8, 1996 at Reel 008827, Frame 0772; change of name from Astra Aktiebolag to AstraZeneca AB, recorded September 6, 2001 at Reel 011933, Frame 0228; assignment from AstraZeneca AB to Medivir AB on September 6, 2001 at Reel 011965, Frame 0237 (Exhibit 2). As shown in Exhibit 2, the recordation on September 6, 2001 corrected an invalid recording attempted on August 30, 2001 (see Reel 011938, Frame 0899). Enclosed as Exhibit 3 is a copy of the Reissue Application Declaration and Power of Attorney appointing the undersigned and Leonard R. Svensson at the undersigned's law firm as agents to transact all business with the USPTO in connection with the '264 patent.

The '264 patent matured from United States Patent Application No. 10/771,259 (the '259 application). As mentioned above, the '259 application was filed as a reissue application of US Patent 6,337,324 which had issued on January 8, 2002, and which had been designated as US Serial No.: 08/612,847 during the national phase of International Application PCT/SE96/00124 and which entered the US national phase by completing the requirements of 35 USC § 371 on March 8, 1996 (Exhibit 4).

The approved product that is relevant to this application is a cream containing 5% Acyclovir and 1% Hydrocortisone for topical administration, referred to herein as "Acyclovir and Hydrocortisone Cream, 5%/1%," or "Approved Product."

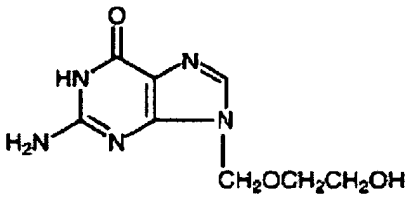
The following information is submitted by Applicants, in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791. The following sections are numbered analogously to the format of 37 C.F.R. §1.740.

(1) Identification of the Approved Product

The approved product Acyclovir and Hydrocortisone Cream, 5%/1%, is a topical formulation of the active ingredients acyclovir and hydrocortisone at a synergistic concentration of 5% acyclovir and 1% hydrocortisone. Acyclovir and Hydrocortisone Cream, 5%/1%, has

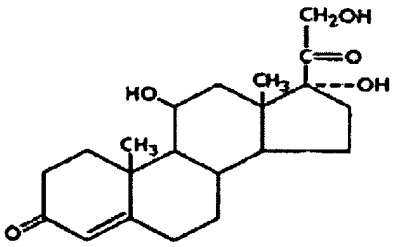
been approved for topical administration for the treatment of recurrent herpes labialis (cold sores).

Acyclovir is designated chemically by INN as 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one. Additional chemical names include, but are not limited to: 2-amino-9-((2-hydroxyethoxy)methyl)-1H-purin-6(9H)-one and 9-[(2-hydroxyethyoxy)methyl]guanine. The chemical structure for acyclovir is:



Acyclovir is synthetic nucleoside analogue. The molecular weight of acyclovir is 225.21 daltons. The empirical formula is $C_8H_{11}N_5O_3$. The maximum solubility of acyclovir in water at 37°C is 2.5 mg/mL. The pKa of acyclovir is 2.27 and 9.25.

Hydrocortisone is designated chemically by INN as pregn-4-ene-3, 20-dione, 11, 17, 21-trihydroxy-(11(beta))-. Additional chemical names include, but are not limited to: (11β)-11,17,21-trihydroxy-pregn-4-ene-3,20-dione and 4-pregnene-11β,17α,21-triol-3,20-dione. The chemical structure for hydrocortisone is:



Hydrocortisone is a glucocorticoid, specifically an anti-inflammatory corticosteroid. The molecular weight of hydrocortisone is 362.47 daltons. The empirical formula is $C_{21}H_{30}O_5$.

Acyclovir and Hydrocortisone Cream, 5%/1%, is supplied as a topical cream, and contains as the active ingredient a synergistic combination of 5% acyclovir, a synthetic nucleoside analogue active against herpes viruses, and 1% hydrocortisone. It also contains the following inactive ingredients: cetostearyl alcohol, mineral oil, Poloxamer 188, propylene glycol, isopropyl myristate, sodium lauryl sulfate, white petrolatum, citric acid, sodium hydroxide and water.

Sodium hydroxide or hydrochloric acid may be added to adjust the pH to approximately pH 5.

(2) Identification of the Federal Statute under which Regulatory Review Occurred

The approved product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(b)).

(3) The Date of Permission for Commercial Marketing

The Approved Product received permission for commercial marketing or use by the Food and Drug Administration ("FDA") pursuant to Section 505(b) of the FFDCA (21 U.S.C. § 355(c)) in a letter dated July 31, 2009 containing the electronic signatures of Debra Birnkrant, M.D., Direction of the Division of Antiviral Products, Office of Antimicrobial Products, Center for Drug Evaluation and Research and Jeffrey S. Murray. A copy of the FDA approval letter is attached as Exhibit 5.

(4) Active Ingredient Statement

Applicant states that the active ingredient of the Approved Product is a synergistic combination of 5% acyclovir and 1% hydrocortisone for the treatment of recurrent herpes labialis.

Acyclovir and Hydrocortisone Cream, 5%/1%, is the first approved product that contains the synergistic combination of 5% acyclovir and 1% hydrocortisone. Please note that the synergistic combination of 5% acyclovir and 1% hydrocortisone, which is shown to have an improved pharmacological effect (see Exhibit 9), is a different active ingredient from 5% acyclovir, which is marketed as Zovirax® (NDA 21-478) and was approved by the U.S. Food and Drug Administration ("FDA"). The synergistic combination of 5% acyclovir and 1% hydrocortisone is also a different active ingredient from 1% hydrocortisone, which was separately approved by the FDA. Accordingly, consistent with Section 2751 of the Manual of Patent Examining Procedure, Acyclovir and Hydrocortisone Cream, 5%/1%, should be considered to have a new single active ingredient which has not been previously approved for commercial marketing and use.

(5) Statement of Timely Filing

This application is timely filed, pursuant to 35 U.S.C. § 156(d)(1) and 37 C.F.R.§ 1.720(f), within the permitted sixty-day (60-day) period that began on July 31, 2009 when the product received permission under 21 U.S.C. § 355(b) and that will expire on September 28, 2009.

(6) Identification of Patent for which Extension is Sought

The expiration date of U.S. Patent No. RE39,264 ("the '264 patent") is February 2, 2016 based on the following:

The patent application that issued as the '264 patent, U.S. Application No. 10/771,259, issued on September 5, 2006 as a Reissued Patent of US 6,337,324 ("the parent '324 patent").

The parent '324 patent issued from an application (08/612,847) that was the national stage filing of PCT Application No. PCT/SE96/00124, filed on February 2, 1996 (Exhibit 4). Thus, the earliest filing date for the '264 patent for purposes of patent term calculation is February 2, 1996, and 20 years from this date is February 2, 2016.

The '264 patent is subject to a terminal disclaimer (Exhibit 7), disclaiming any patent term beyond the expiration of the full term of US Patent No. 6,068,860 ('860; Exhibit 6). The expiration date of the '860 patent is February 2, 2016, which is 20 years from its PCT international filing date, of February 2, 2016. Consequently, the terminal disclaimer has no effect on the patent term and the expiration date of the '264 patent is February 2, 2016.

Johan Harmenberg and Ann Harriet Margareta Kristofferson are named as inventors.

(7) Patent Copy

A complete copy of U.S. Patent No. RE39,264 E is attached as Exhibit 1.

(8) Post-Issuance Activity Statement

United States Patent No. RE39,264 E is subject to a Terminal Disclaimer (Exhibit 7).

United States Patent No. RE39,264 E has not been re-examined, nor has the parent '324 patent, therefore no reexamination certificate has been issued.

No certificates of correction have been filed for U.S. Patent No. RE39,264 E, however a certificate of correction was filed for the parent '324 patent (Exhibit 12).

The first maintenance fee (i.e. the 4th year) for the parent '324 patent (i.e. U.S. Patent No. 6,337,324) was paid June 9, 2005, as shown by the Patent Bibliographic Data Sheet and the USPTO Maintenance Fee Statement for the parent '324 patent, both dated September 25, 2009, and both found in Exhibit 13.

The first maintenance fee (i.e. the 8th year) for U.S. Patent No. RE39,264 E was paid June 15, 2009, as shown by the Patent Bibliographic Data Sheet and the USPTO Maintenance Fee Statement for this patent, both dated September 15, 2009, and both found in Exhibit 8. The next maintenance fee is not yet due. The payment window for the next maintenance fee (12th year fee) does not open until January 8, 2013. Accordingly, there are no unpaid maintenance fees for this patent.

(9) Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product

U.S. Patent No. RE39,264 E claims the Approved Product. Specifically, compound claims 2, 4, 7 and 13-16 read on the Approved Product as do method claims 18, 20, 23, 24, 25, 27-31 and 33-37.

Please note that claim 29 incorrectly recites claim 40 as its antecedent. This is an error that had gone undetected until now. Specifically, when the claims were allowed at the end of examination, issued claim 37 was numbered "claim 40." When the claims were renumbered for issuance, while "claim 40" was properly renumbered as claim 37, the dependency in claim 29 referring to "claim 40" was apparently overlooked and not corrected to read "claim 37." A certificate of correction will be requested to correct this error.

Pursuant to 37 C.F.R. § 1.740(a)(9), a showing which demonstrates the manner in which at least one claim reads on the approved product is set forth herein below.

CLAIM	ELEMENTS
2. A pharmaceutical composition for topical administration *to treat recurrent herpes infections* comprising, as *sole active drug substances*, a [synergistic] combination of *an* [topically acceptable] antiviral [substance] *ingredient* selected from the group consisting	The active ingredient (also commonly referred to as the "effective ingredient") of Acyclovir and Hydrocortisone Cream, 5%/1% is a synergistic combination of the antiviral acyclovir and anti-inflammatory glucocorticoid hydrocortisone.

of *foscarnet*, acyclovir, [cidofovir, desciclovir, famciclovir, ganciclovir, lobucavir,] penciclovir, [PMEA, valacyclovir, 2242, PAA, PFA] and 9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (H2G), or [an ester,] a salt [or solvate] thereof and an anti-inflammatory glucocorticoid *ingredient selected from the group consisting of hydrocortisone and esters thereof,* in a pharmaceutically acceptable carrier, *wherein said combination of antiviral and glucocorticoid is more effective in treating said herpes infections than either ingredient alone.*	The Acyclovir and Hydrocortisone Cream, 5%/1% is significantly more efficacious (i.e. has a synergistic effect) than either acyclovir or hydrocortisone alone (see Exhibit 9)
18. A method for [the prophylaxis and/or treatment of] *treating recurrent* herpesvirus infections of the skin or mucous membranes in mammals *having or identified as being at risk of developing said infections* comprising topical*ly* administ[ration]*ring thereto, as sole active drug substances and* in combination or in sequence, [of a therapeutically synergistic dose of] [a topically acceptable] *an* antiviral [substance] *ingredient* selected from the group consisting of *foscarnet*, acyclovir, [cidofovir, desiciclovir, famciclovir, ganciclovir, lobucovir,] penciclovir, [PMEA, valacyclovir, 2242, PAA, PFA] and *9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine* (H2G), or [an	As discussed above, Acyclovir and Hydrocortisone Cream, 5%/1% is a pharmaceutical composition containing a synergistic combination of the antiviral acyclovir and anti-inflammatory glucocorticoid hydrocortisone as the active ingredient. The Acyclovir and Hydrocortisone Cream, 5%/1% is significantly more efficacious (i.e. has a synergistic effect) than either acyclovir or hydrocortisone alone (see Exhibit 9) and is used to treat recurrent herpesvirus infections.

ester,] *a* salt [or solvate] thereof and an anitiinflammatory glucocorticoid *ingredient selected from the group consisting of hydrocortisone and esters thereof,* in a pharmaceutically acceptable carrier, *wherein said antiviral and glucocorticoid are more effective in treating said herpesvirus infections than either ingredient alone.*	

(10) Statement of the Relevant Dates to Determine the Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Resources to determine the applicable regulatory review period are as follows:

(i)The patent for which extension of term is sought claims a human drug product.

(A) An original Investigational New Drug Application ("IND") was filed on June 18, 1999, and assigned IND No. 58,500. Applicants received a letter from the FDA stating that the IND application was received on June 21, 1999. A copy of this letter, dated July 9, 1999, which acknowledged receipt of the IND is attached as Exhibit 10. Accordingly, IND No. 58,500 became effective 30 days from June 21, 1999, which is July 21, 1999.

(B) A New Drug Application ("NDA") was submitted on September 30, 2008 and was acknowledged as received on October 1, 2008 in a letter from the FDA dated July 31, 2009 (Exhibit 5). This letter indicated that the NDA was assigned number 22-436. Accordingly, the NDA was initially submitted on October 1, 2008.

(C) The NDA 22-436 was approved on July 31, 2009 (Exhibit 5).

(11) Brief Description of Activities Undertaken During the Regulatory Review Period

In accordance with 37 C.F.R. § 1.740(a)(11), enclosed as Exhibit 11 is a chronology of the major communications between the FDA and the Marketing Applicant in IND No. 58,500 and NDA No. 22-436 during the applicable regulatory review period.

(12) Opinion of Eligibility for Extension

Applicants are of the opinion that U.S. Patent No. RE39,264 E is eligible for extension under 35 U.S.C. §156 and 37 C.F.R. §1.720 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. §156(a) and 37 C.F.R. §1.720(a)

U.S. Patent No. RE39,264 E claims, a synergistic combination of 5% acyclovir and 1% hydrocortisone, the active ingredient of a human drug product, pharmaceutical compositions containing the active ingredient and a method of using it as discussed above in section (9).

(b) 35 U.S.C. §156(a)(1) and 37 C.F.R. §1.720(g)

The term of U.S. Patent No. RE39,264 E is currently set to expire on February 2, 2016 and, therefore, has not expired before the submission of this application.

(c) 35 U.S.C. §156(a)(2) and 37 C.F.R. §1.720(b)

The term of U.S. Patent No. RE39,264 E has never been extended.

(d) 35 U.S.C. §156(a)(3) and 37 C.F.R. §1.720(c)

The application for extension of the term of U.S. Patent No. RE39,264 E is submitted by the authorized attorney of the owners of record thereof in accordance with the requirements of 35 U.S.C. §156(d) and 37 C.F.R. §1.740.

(e) 35 U.S.C. §156(a)(4) and 37 C.F.R. §1.720(d)

The approved product, Acyclovir and Hydrocortisone Cream, 5%/1%, has been subjected to a regulatory review period before its commercial marketing or use, as evidenced by the approval letter of July 31, 2009 from the FDA to Medivir, AB. (Exhibit 5).

(f) 37 C.F.R. §1.720(h)

No other patent has been extended for the same regulatory review period for the approved product, Acyclovir and Hydrocortisone Cream, 5%/1%.

(g) 35 U.S.C. §156(a)(5)(A) and 37 C.F.R. §1.720(e)(1)

The permission for the commercial marketing or use of the approved product, Acyclovir and Hydrocortisone Cream, 5%/1%, is the first received permission for commercial marketing or use of Acyclovir and Hydrocortisone Cream, 5%/1%, under the provision of law under which the applicable regulatory review occurred. (See also section (4) above).

Length of Extension Claimed Under 37 C.F.R. §1.740(a)(12) and Determination of Length of Extension Under 37 C.F.R. § 1.775

The length of extension of the patent term of U.S. Patent No. RE39,264 E, now expiring on February 2, 2016, requested by Applicants is 1533 days, which length was calculated in accordance with 37 C.F.R. §1.775 as follows:

(a) The regulatory review period under 35 U.S.C. §156(g)(1)(B) began on July 21, 1999 (the effective date of the IND No. 58,500) and ended on July 31, 2009 (NDA approval letter date), amounting to a total of 3664 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. §156(g)(1)(B)(i), the "Testing Period," began on July 21,1999 and ended on October 1, 2008 with submission of the NDA No. 22-436 which is 3361 days;

(ii) The period for review under 35 U.S.C. §156(g)(1)(B)(ii), the "Application Period," began on October 1, 2008 and ended on July 31, 2009, which is 303 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as described in subparagraph (a) immediately above (3664 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (January 8, 2002), i.e., 902 days, and

(ii) The number of days during which the Applicants did not act with due diligence, i.e., 0 days, and

(iii) One-half of the number of days remaining in the period in subparagraph (a)(i) immediately above after subtracting the number of days in the subparagraphs immediately above denoted as (b)(i) and (b)(ii), which is one-half of (3361 - [902 + 0]) or 1229 days;

Which results in a period of 3664 - [902 + 0 + 1229 days] = 1533 days.

(c) The number of days as determined in subparagraph (b) immediately above, when added to the original term (February 2, 2016), would result in the date of April 14, 2020.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (July 31, 2009) would result in the date of July 31, 2023.

(e) The earlier date as determined by the subparagraphs immediately above denoted as (c) and (d) is April 14, 2020.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. RE39,264 E (February 2, 2016), results in the date February 2, 2021.

(g) The earlier date as determined in the subparagraphs immediately above denoted as (e) and (f) is April 14, 2020.

Conclusion: Accordingly, U.S. Patent No. RE39,264 E is eligible for a patent term extension of 1533 days.

(13) Duty of Disclosure Acknowledgement Under 37 C.F.R. §1.740(a)(13)

Applicants acknowledge a duty to disclose to the Commissioner of Patent and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) Fee Charge

The prescribed fee of $1,120 under 37 C.F. R. § 1.20(j)(1) for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 02-2448 as authorized in the attached transmittal letter, submitted in triplicate. The Director is hereby authorized to charge our deposit account No. 02-2448 under docket number 1718-0214P for any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith, or with any paper herein after filed in the application/patent by this firm.

(15) Correspondence Address Required by 37 C.F.R. §1.740(a)(15)

All correspondence relating to this application for patent term extension should be addressed to:

Susan W. Gorman
Birch, Stewart, Kolasch & Birch, LLP
P.O. Box 747
Falls Church, VA 22040

Telephone Number (858) 792-8855

(16) Certification Under 37 C.F.R. §1.740(b)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted as one original and two copies thereof in accordance with 37 C.F.R. §1.740(b).

Dated: September 25, 2009

Respectfully submitted,

By _____
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Patent No. (if known): RE39,264 E

Attorney Docket No.: 1718-0214P

Certificate of Express Mailing Under 37 CFR 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail, Airbill No. EV 943145378 US in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
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on September 28, 2009
Date

Alison Lalonde
Signature

Alison Lalonde
Typed or printed name of person signing Certificate

Registration Number, if applicable

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Note: Each paper must have its own certificate of mailing, or this certificate must identify each paper separately:

Corrected Request for Patent Term Extension (16 pages)
Transmittal Form (1 page)
Return Receipt Postcard
Fee Transmittal (1 page)
Exhibit 1 (12 pages) ; Exhibit 2 (2 pages)
Exhibit 3 (2 pages); Exhibit 4 (13 pages)
Exhibit 5 (18 pages); Exhibit 6 (14 pages)
Exhibit 7 (2 pages); Exhibit 8 (2 pages)
Exhibit 9 (11 pages); Exhibit 10 (2 pages)
Exhibit 11 (9 pages); Exhibit 12 (1 page)
Exhibit 13 (2 pages)

1st Page

EXHIBIT 1

US00RE39264E

(19) **United States**

(12) **Reissued Patent**

Harmenberg et al.

(10) **Patent Number: US RE39,264 E**

(45) **Date of Reissued Patent: Sep. 5, 2006**

(54) **PHARMACEUTICAL COMBINATION**

(75) Inventors: **Johan Harmenberg**, Stockholm (SE); **Ann Harriet Margareta Kristofferson**, Sodertaklje (SE)

(73) Assignee: **Medivir AB**, Huddinge (SE)

(21) Appl. No.: **10/771,259**

(22) PCT Filed: **Feb. 2, 1996**

(86) PCT No.: **PCT/SE96/00124**

§ 371 (c)(1),
(2), (4) Date: **Mar. 8, 1996**

(87) PCT Pub. No.: **WO96/24355**

PCT Pub. Date: **Aug. 15, 1996**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **6,337,324**
Issued: **Jan. 8, 2002**
Appl. No.: **08/612,847**
Filed: **Mar. 8, 1996**

(51) **Int. Cl.**
A61K 31/56 (2006.01)

(52) **U.S. Cl.** **514/171**; 514/75; 514/81; 514/82; 514/85; 514/120; 514/179

(58) **Field of Classification Search** 514/171, 514/75, 81, 82, 85, 120, 179
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,317,384	A	*	5/1967	Underwood	514/50
4,512,978	A	*	4/1985	Inwood	424/642
4,610,868	A	*	9/1986	Fountain et al.	424/1.21
4,902,678	A	*	2/1990	Smith	514/45
4,942,031	A		7/1990	Levin	
5,023,090	A		6/1991	Levin	
5,656,301	A		8/1997	Levin	
5,856,364	A	*	1/1999	Martin	514/724
6,068,860	A	*	5/2000	Carlsson et al.	424/601
6,514,980	B1		2/2003	Boyd	514/263.31
2004/0185433	A1		9/2004	Boyd	435/5

FOREIGN PATENT DOCUMENTS

AU	0636255	*	5/1992
AU	636255	*	4/1993
EP	0350287	*	1/1990
EP	0594223	*	4/1994
WO	9219244	*	11/1992
WO	9503805	*	2/1995
WO	9527501	*	10/1995

OTHER PUBLICATIONS

Alenius, S., et al; Therapeutic Effects of Foscarnet Sodium and Acyclovir on Cutaneous Infections due to Herpes Simplex Virus Type 1 in Guinea Pigs, J. Inf. Dis. 1982; 145:569–73.*

The Human Herpesviruses, ed. Roizman et al. 1993, Whitely, Richard et al; The epidemiology and Clinical Manifestations of Herpes Simplex Virus Infections.*

Kristofferson, A. et al.; Limited Efficacy of Inhibitors of Herpes Simplex Virus DNA Synthesis in Murine Models of Recrudescent Disease, J. Gen. Virol. (1988), 69, 1157–1166.*

Schinazi, R.F. et al; Studies in Vitro and In Vivo of Combinations of Antivirals and Antiinflammatory Agents in Relation to the Treatment of Herpes Simplex Viruses, Current Chemotherapy and Immunotherapy, 12th Int. Congress, Florence, Jul. 1981.*

From Chemical Abstracts, vol. 112, nr. CA:125021: Loftsson, T.; Effect of choline esters and oleic acid on the penetration of acyclovir, estradiol, hydrocortisone, nitroglycerin, retinoic acid and trifluorothymidine across hairless mouse skin in vitro, Acta Pharm. Nor. (1989), 1(5), 279–86.*

From Chemical Abstracts, vol. 112, nr 4 (dissertation): Choi, Hoo Kyun: Enhanced transdermal delivery of propanolol, hydrocortisone, acyclovir and peptide–type drugs (1989).*

Power, W J et al, Acyclovir ointment plus topical betamethasone or placebo in first episode disciform keratitis, British Journal of Opthalmology 1992; 76:711–713.*

McGill, J. Herpes zoster ocular infection, Scand. J. Infect. Dis. Suppl. 46: 85–88, 1985.*

ABPI Compendium of Data Sheets and Summaries of Product Characteristics, 1996–97, Datapharm Publications Ltd., pp. 390 and 1271.*

Bekow, et al., the Merck Manual of Diagnosis and Therapy, 14th Edition, pp. 2023–2025 (1982).*

Chemical Abstract No. 97: 156002r from Schinazi et al., Curr. Chemother. Immunother. 2, 1085–1087 (1982).*

Merck Index 10th Ed #140, #4135, #1435, 1984.*

Notter et al., 89 CA:157769t, 1978.*

Chemical Abstracts 103:572328, "The antiinflammatory effect of budesonide", Hiroi et al, from STN File CAPLUS database (first publicly available Nov. 30, 1985).*

F.Y. Aoki et al., "Topical glucorticoid alone or combined with 10% acyclovir . . . ," XP–001117608. Abstract and Clarified Text. (1988).

W.J. Power et al., "Acyclovir ointment plus topical betamethasone or placebo . . . ," British Journal of Ophthalmology, 1992, vol. 76, pp. 711–713.

J. McGill, "Herpes zoster ocular infection," Scand J. Infect. Dis., Suppl., 1958,47, pp. 85–88.

Harmenburg, J. et al., "ME–609: a treatment for recurrent herpes . . . ," International Medical Press, 2003, pp. 205–215.

Harmenburg, J. et al., "ME–609: a treatment for recurrent herpes . . . ," Manuscript, pp. 1–30. (2003).

Evans, T.G. et al, "Double–blind randomized, placebo–controlled . . . ," Antimicrobial Agents and Chemotherapy, Jun. 2002, pp. 1870–1874.

* cited by examiner

Primary Examiner—Frederick Krass

(74) *Attorney, Agent, or Firm*—Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

The invention relates to pharmaceutical compositions for topical administration comprising a topically acceptable antiviral substance and an antiinflammatory glucocorticoid in a pharmaceutically acceptable carrier. The pharmaceutical composition can be used in the prophylactic and curative treatment of herpesvirus infections in mammals including man. The invention also relates to the use of a combination of a topically acceptable antiviral substance and an antiinflammatory glucocorticoid for the manufacture of a medicament for said prophylactic and curative treatment.

27 Claims, 3 Drawing Sheets

EXHIBIT 2

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 4

Patent #: 6337324 **Issue Dt:** 01/08/2002 **Application #:** 08612847 **Filing Dt:** 03/08/1996

Inventors: JOHAN G. HARMENBERG, ANN H.M. KRISTOFFERSON

Title: NOVEL PHARMACEUTICAL COMBINATION

Assignment: 1

Reel/Frame: 008827/0772 **Recorded:** 03/08/1996 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors: HARMENBERG, JOHAN GEOR **Exec Dt:** 02/12/1996

KRISTOFFERSON, ANN HARRIET MARGARETA **Exec Dt:** 02/12/1996

Assignee: ASTRA AKTIEBOLAG
S-151 85 SODERTALJE, SWEDEN

Correspondent: WHITE & CASE
EDWARD V. FILARDI, ESQ.
PATENT DEPARTMENT
1155 AVENUE OF THE AMERICAS
NY, NY 10036

Assignment: 2

Reel/Frame: 011933/0228 **Recorded:** 09/06/2001 **Pages:** 5

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

Assignor: ASTRA AKTIEBOLAG **Exec Dt:** 01/03/2000

Assignee: ASTRAZENECA AB
S-151 85 SODERTALJE, SWEDEN

Correspondent: WHITE & CASE LLP
RICHARD J. STERNER- PATENT DEPARTMENT
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

Assignment: 3

Reel/Frame: 011938/0899 **Recorded:** 08/30/2001 **Pages:** 5

Conveyance: INVALID RECORDING. SEE RECORDING AT REEL 011965, FRAME 0239. RE-RECORDED TO CORRECT RECORDATION DATE.

Assignor: ASTRAZENECA AB **Exec Dt:** 08/07/2001

Assignee: MEDIVIR AB
LUNASTIGEN 7
S-141 44 HUDDINGE, SWEDEN

Correspondent: WHITE & CASE LLP
RICHARD J. STERNER
PATENT DEPARTMENT
1155 AVENUE OF THE AMERICAS
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Assignment: 4

Reel/Frame: 011965/0237 **Recorded:** 09/06/2001 **Pages:** 5

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: ASTRAZENECA AB **Exec Dt:** 08/07/2001

Assignee: MEDIVIR AB
LUNASTIGEN 7
S-141 44 HUDDINGE, SWEDEN

Correspondent: WHITE & CASE, LLP
RICHARD J. STERNER
1155 AVENUE OF THE AMERICA
NEW YORK, NY 10036

Search Results as of: 09/21/2009 12:00 PM
If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350.
Web interface last modified: October 18, 2008 v.2.0.2

EXHIBIT 3

PTO/SB/52 (06-03)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REISSUE APPLICATION DECLARATION BY THE ASSIGNEE

Docket Number (optional): 1718-0214P

I hereby declare that:

The residence, mailing address and citizenship of the inventors are stated below.

I am authorized to act on behalf of the following assignee: **MEDIVIR AB**

and the title of my position with said assignee is: **CEO & President**

and the title of my position with said assignee is: _____

The entire title to the patent identified below is vested in said assignee.

Inventor	Citizenship
Johan Georg HARMENBERG	**SWEDEN**

Residence/Mailing Address: **Kurlavagen 94, S-115 22 Stockholm, SWEDEN**

Inventor	Citizenship
Ann Harriet Margareta KRISTOFFERSON	**SWEDEN**

Residence/Mailing Address: **Majorpsvagen 8, S-152 70 Sodertalje, SWEDEN**

☐ Additional inventors are named on separately numbered sheets attached hereto.

Patent	Date of Patent Issued
6,337,324	**January 8, 2002**

Title of Invention: **PHARMACEUTICAL COMBINATION**

I believe said inventor(s) to be the original and first inventor(s) of the subject matter which is described and claimed in said patent, for which a reissue patent is sought on the invention entitled:
PHARMACEUTICAL COMBINATION

the specification of which

☒ is attached hereto.

☐ was filed on _____ as reissue application number _____
and was amended on _____
(If applicable)

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

☐ I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b). Attached is form PTO/SB/2B (or equivalent) listing the foreign applications.

I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below. (Check all boxes that apply.)

☐ by reason of a defective specification or drawing,

☒ by reason of the patentee claiming more or less than he had the right to claim in the patent.

☐ by reason of other errors.

PTO/SB/52 (06-03)
Approved for use through 01/31/2004. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REISSUE APPLICATION DECLARATION BY THE ASSIGNEE	Docket Number (Optional) 1718-0214P

At least one error upon which reissue is based is described as follows:
Claim 1 is too broad and should be amended as shown in the accompanying Amendment under 37 CFR 1.173(b).

[Attach additional sheets, if needed.]
All errors corrected in this reissue application arose without any deceptive intention on the part of the applicant.

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact

Name(s)	Registration Number
Leonard R. Svensson	**#30,330**
Susan W. Gorman	**#47,604**

Correspondence Address: Direct all communications about the application to:

☒ Customer Number **02292**

OR

☐ Firm or Individual Name					
Address					
Address					
City		State		Zip	
Country					
Telephone		Fax			

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.

Full name of person signing (given name, family name)
Lars Adlersson

Signature	Date
Lars Adlersson	2 February 2004

Address of Assignee
Lunastigen 7, S-141 44 Huddinge, SWEDEN

1st page

EXHIBIT 4

US006337324B1

(12) **United States Patent**
Harmenberg et al.

(10) **Patent No.: US 6,337,324 B1**
(45) **Date of Patent: *Jan. 8, 2002**

(54) **PHARMACEUTICAL COMBINATION**

(75) Inventors: **Johan Georg Harmenberg**, Stockholm; **Ann Harriet Margareta Kristofferson**, Södertälje, both of (SE)

(73) Assignee: **Medivir, AB**, Huddinge (SE)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **08/612,847**

(22) PCT Filed: **Feb. 2, 1996**

(86) PCT No.: **PCT/SE96/00124**

§ 371 Date: **Mar. 8, 1996**

§ 102(e) Date: **Mar. 8, 1996**

(87) PCT Pub. No.: **WO96/24355**

PCT Pub. Date: **Aug. 15, 1996**

(30) **Foreign Application Priority Data**

Feb. 6, 1995 (WO) PCT/SE95/00114

(51) **Int. Cl.**[7] **A61K 31/56**

(52) **U.S. Cl.** **514/171**; 514/75; 514/81; 514/82; 514/85; 514/120; 514/179

(58) **Field of Search** 514/179, 171, 514/75; 518/85, 81, 82, 120

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,317,384 A		5/1967	Underwood	167/58
4,512,978 A		4/1985	Inwood	424/145
4,610,868 A		9/1986	Fountain et al.	424/1.1
6,068,860 A	*	5/2000	Carlsson et al.	424/601

FOREIGN PATENT DOCUMENTS

AU	0636255	*	5/1992	A61K/31/66
AU	636255		4/1993	A61K/31/66
EP	0350287		1/1990	A61K/31/70
EP	0594223		4/1994	A61K/31/70
WO	9219244		11/1992	A61K/31/57
WO	9503805		2/1995	A61K/31/52
WO	9527501		10/1995	A61K/38/21

OTHER PUBLICATIONS

Alenius, S., et al; Therapeutic Effects of Foscarnet Sodium and Acyclovir on Cutaneous Infections due to Herpes Simplex Virus Type 1 in Guinea Pigs, J. Inf. Dis. 1982; 145:569–73.

The Human Herpesviruses, ed. Roizman et al. 1993, Whitely, Richard et al.; The epidemiology and Clinical Manifestations of Herpes Smplex Virus Infections.

Kristofferson, A. et al.; Limited Efficacy of Inhibitors of Herpes Simplex Virus DNA Synthesis in Murine Models of Recrudescent Disease, J. Gen. Virol. (1988), 69, 1157–1166.

Schinazi, R.F. et al; Studies In Vitro and In Vivo of Combinations of Antivirals and Antiinflammatory Agents in Relation to the Treatment of Herpes Simplex Viruses, Current Chemotherapy and Immunotherapy, 12th Int. Congress, Florence, Jul. 1981.

From Chemical Abstracts, vol. 112, nr. CA:125021: Loftsson, T.; Effect of choline esters and oleic acid on the penetration of acyclovir, estradiol, hydrocortisone, nitroglycerin, retinoic acid and trifluorothymidine across hairless mouse skin in vitro, Acta Pharm. Nor. (1989), 1(5), 279–86.

From Chemical Abstracts, vol. 112, nr 4, (dissertation): Choi, Hoo Kyun: Enhanced transdermal delivery of propanolol, hydrocortisone, acyclovir and peptide–type drugs (1989).

Power, W J et al., Acyclovir ointment plus topical betamethasone or placebo in first episode disciform keratitis, British Journal of Ophtalmology 1992; 76:711–713.

McGill, J. Herpes zoster ocular infection, Scand. J. Infect. Dis. Suppl. 46: 85–88, 1985.

ABPI Compendium of Data Sheets and Summaries of Product Characteristics, 1996–97, Datapharm Publications Ltd., pp. 390 and 1271.

Berkow, et al., The Merck Manual of Diagnosis and Therapy, 14th Edition, pp. 2023–2025 (1982).

Chemical Abstract No. 97: 156002r from Schinazi, et al., Curr. Chemother. Immunother. 2, 1085–1087 (1982).*

Merck Index 10th Ed #140, #4135, #1435, 1984.*

Notter et al, 89 CA:157769t, 1978.*#jf139##

Primary Examiner—Frederick Krass
(74) *Attorney, Agent, or Firm*—White & Case LLP

(57) **ABSTRACT**

The invention relates to pharmaceutical compositions for topical administration comprising a topically acceptable antiviral substance and an antiinflammatory glucocorticoid in a pharmaceutically acceptable carrier. The pharmaceutical composition can be used in the prophylactic and curative treatment of herpesvirus infections in mammals including man. The invention also relates to the use of a combination of a topically acceptable antiviral substance and an antiinflammatory glucocorticoid for the manufacture of a medicament for said prophylactic and curative treatment.

36 Claims, 3 Drawing Sheets

EXHIBIT 5

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-436

NDA APPROVAL

Medivir AB
c/o B&H Consulting Services, Inc.
Attn: Elizabeth Dupras
55 North Gaston Avenue
Somerville, NJ 08876

Dear Ms. Dupras:

Please refer to your new drug application (NDA) dated September 30, 2008, received October 1, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Acyclovir and Hydrocortisone Cream, 5%/1%, Topical.

We acknowledge receipt of your submissions dated:

October 28, 2008	April 16, 2009	May 8, 2009
October 30, 2008	April 17, 2009	June 2, 2009
November 19, 2008	April 20, 2009	June 29, 2009
December 5, 2008	April 23, 2009	July 20, 2009
December 23, 2008	April 30, 2009	July 30, 2009

This new drug application provides for the use of Acyclovir and Hydrocortisone Cream for the early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and adolescents (12 years of age and older).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-436.**"

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-436.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages less than 6 years of age because necessary studies are impossible or highly impracticable and the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group. This is because of the pathophysiology and epidemiology of the disease. Herpes labialis in children less than 6 years of age is generally a primary infection, and not a recurrence.

We are deferring submission of your pediatric study for ages greater than 6 years to less than 12 years for this application because this product is ready for approval for use in adults and adolescents (12 years of age and older).

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1500-1. Deferred pediatric study under PREA for the treatment of recurrent herpes labialis in pediatric patients ages greater than 6 years to less than 12 years.

Final Report Submission: May 1, 2013

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment**".

We note that you have fulfilled the pediatric study requirement for ages greater than 12 years for this application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call David Araojo, Pharm.D., Regulatory Project Manager, at (301) 796-0669.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure (Package Insert, Patient Package Insert, Carton and Container Labels)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Acyclovir and Hydrocortisone Cream safely and effectively. See full prescribing information for Acyclovir and Hydrocortisone Cream.

Acyclovir and Hydrocortisone Cream for topical use

Initial U.S. Approval: 2009

INDICATIONS AND USAGE

Acyclovir and Hydrocortisone Cream, a combination of acyclovir and hydrocortisone, is indicated for the early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and adolescents (12 years of age and older) (*1*).

DOSAGE AND ADMINISTRATION

Topically apply Acyclovir and Hydrocortisone Cream 5 times per day for 5 days. Therapy should be initiated as early as possible after the first signs and symptoms (i.e., during the prodrome or when lesions appear) (*2*).

DOSAGE FORMS AND STRENGTHS

Topical cream containing 5% acyclovir and 1% hydrocortisone (*3*).

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Only for topical use of recurrent herpes labialis on the lips and around the mouth (*5*).

ADVERSE REACTIONS

The following most common adverse reactions (< 1%) were local skin reactions (*6.2*):

- Drying or flaking of the skin; burning or tingling, erythema; pigmentation changes.

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

No drug interaction studies have been performed with Acyclovir and Hydrocortisone Cream.

USE IN SPECIFIC POPULATIONS

- Immunocompromised Patients: Benefit has not been adequately assessed (8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Acyclovir and Hydrocortisone Cream is indicated for the early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and adolescents (12 years of age and older).

2 DOSAGE AND ADMINISTRATION

Topically apply Acyclovir and Hydrocortisone Cream 5 times per day for 5 days. Therapy should be initiated as early as possible after the first signs and symptoms (i.e., during the prodrome or when lesions appear).
For each dose, topically apply a quantity of Acyclovir and Hydrocortisone Cream sufficient to cover the affected area, including the outer margin. Avoid unnecessary rubbing of the affected area to avoid aggravating or transferring the infection. For adolescents 12 years of age and older, the dosage is the same as in adults.

3 DOSAGE FORMS AND STRENGTHS

Each gram of Acyclovir and Hydrocortisone Cream contains 5% (w/w) acyclovir and 1% (w/w) hydrocortisone in an aqueous cream base.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 General

Acyclovir and Hydrocortisone Cream is intended for cutaneous use only for herpes labialis of the lips and around the mouth. Acyclovir and Hydrocortisone Cream should not be used in the eye, inside the mouth or nose, or on the genitals.
There are other orofacial lesions, including bacterial and fungal infections, which may be difficult to distinguish from a cold sore. Patients should be encouraged to seek medical advice when a cold sore fails to heal within 2 weeks.
Acyclovir and Hydrocortisone Cream has a potential for irritation and contact sensitization [*see Adverse Reactions (6)*].

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

The safety data derived from Acyclovir and Hydrocortisone Cream clinical studies reflects exposure to Acyclovir and Hydrocortisone Cream in 1002 subjects with recurrent herpes labialis treated 5 times daily for 5 days. The majority of the adverse reactions were local skin reactions and occurred in the area of the application site.

6.2 Adverse Reactions in Clinical Studies

Because clinical studies are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical studies and may not reflect the rates observed in clinical practice.

The majority of the adverse reactions were local and occurred in the area of the application site.

Skin and Subcutaneous Tissue Disorders

The following most common adverse reactions (< 1%) were local skin reactions, and occurred in the area of the application site:

-Drying or flaking of the skin; burning or tingling following application; erythema; pigmentation changes; application site reaction including signs and symptoms of inflammation.

Contact dermatitis following application has been observed when applied under occlusion in dermal safety studies. Where contact sensitivity tests have been conducted, the reactive substances were hydrocortisone or a component of the cream base.

A study enrolling 225 healthy adults was conducted to evaluate the contact sensitization potential of Acyclovir and Hydrocortisone Cream using repeat insult patch testing methodology. Of 205 evaluable subjects, one confirmed case (0.5%) of sensitization to hydrocortisone and 2 additional cases (1.0%) of possible sensitization to the Acyclovir and Hydrocortisone Cream base were identified. Additionally, one subject developed a contact allergy in the photosafety study to propylene glycol, one of the inactive ingredients of the cream base.

Dermal tolerance was assessed in a 21-day cumulative irritation study in 36 healthy subjects. Acyclovir and Hydrocortisone Cream, its cream base and Zovirax® (acyclovir) Cream 5% all showed a high and cumulative irritation potential under occlusive and semi-occlusive conditions.

Photoallergic potential and phototoxicity were assessed in two studies in 50 and 30 healthy volunteers, respectively. No photoallergic or phototoxicity potential was identified for Acyclovir and Hydrocortisone Cream.

7 DRUG INTERACTIONS

No drug interaction studies have been performed with Acyclovir and Hydrocortisone Cream.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category B

Teratogenic Effects:

Acyclovir was not teratogenic in the mouse, rabbit or rat at exposures greatly in excess of human exposure. There are no adequate and well-controlled studies of systemic acyclovir in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy between 1984 and 1999 followed 749 pregnancies in women exposed to systemic acyclovir during the first trimester of pregnancy resulting in 756 outcomes. The occurrence rate of birth defects approximated that found in the general population. However, the size of the registry was insufficient to evaluate the risk for less common defects or to permit reliable or definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses.

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Animal reproduction studies have not been conducted with Acyclovir and Hydrocortisone Cream. No studies have been performed in pregnant women. Systemic exposure of acyclovir and hydrocortisone following topical administration of Acyclovir and Hydrocortisone Cream is minimal.

8.3 Nursing Mothers

It is not known whether topically applied acyclovir or hydrocortisone is excreted in breast milk. Systemic exposure following topical administration of either drug is expected to be below detection limits. Because many drugs are excreted in human milk, caution should be exercised when Acyclovir and Hydrocortisone Cream is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric subjects less than 12 years of age have not been established.

8.5 Geriatric Use

In clinical studies, there were insufficient subjects above 65 years of age to reach a firm conclusion regarding safety and efficacy of Acyclovir and Hydrocortisone Cream in this group, although the available results were similar to lower age subjects.

8.6 Immunocompromised Subjects

Even though the safety of Acyclovir and Hydrocortisone Cream has been studied in immunocompromised subjects, data are insufficient to support use in this population. Immunocompromised subjects should be encouraged to consult a physician concerning the treatment of any infection.

Benefit has not been adequately assessed in immunocompromised patients. A randomized, double-blind study was conducted in 107 immunocompromised subjects with stable HIV infection and recurrent herpes labialis. Subjects had on average 3.7 episodes of herpes labialis in the previous 12 months. The median age was 30 years (range 19 to 64 years), 46% were female, and all Caucasian. Median CD4+ T-cell count at screening was 344/mm^3 (range 100-500/mm^3). Subjects were treated with Acyclovir and Hydrocortisone Cream or 5% acyclovir in Acyclovir and Hydrocortisone Cream vehicle. The primary objective was to exclude a doubling of the healing time in either treatment arm. The mean healing time for cold sores was similar between the two treatment groups: 6.6 days for Acyclovir and Hydrocortisone Cream and 6.9 days for 5% acyclovir in Acyclovir and Hydrocortisone Cream vehicle.

10 OVERDOSAGE

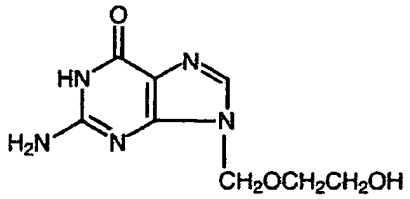
Overdosage by topical application of Acyclovir and Hydrocortisone Cream is unlikely because of minimal systemic exposure [*see Clinical Pharmacology- Pharmacokinetics (12.3)*].

11 DESCRIPTION

Acyclovir and Hydrocortisone Cream contains acyclovir, a synthetic nucleoside analogue active against herpes viruses, and hydrocortisone, an anti-inflammatory corticosteroid, combined in a cream for topical administration. Each gram of Acyclovir and Hydrocortisone Cream contains 5% (w/w) of acyclovir, 1% (w/w) of hydrocortisone and the following inactive ingredients: cetostearyl alcohol, mineral oil, Poloxamer 188, propylene glycol, isopropyl myristate, sodium lauryl sulfate, white petrolatum, citric acid, sodium hydroxide and water. Sodium hydroxide or hydrochloric acid may be added to adjust the pH to approximately pH 5.

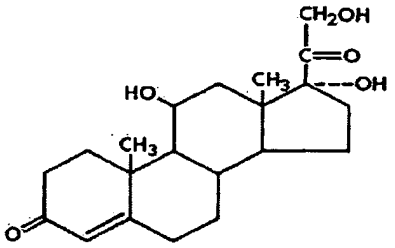
Acyclovir, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin- 6-one, is a synthetic nucleoside analogue active against herpes viruses. The maximum solubility of acyclovir in water at 37°C is 2.5 mg/mL. The pKa's of acyclovir are 2.27 and 9.25. Its empirical formula is $C_8H_{11}N_5O_3$. The structural formula is provided in Figure 1:

Figure 1: Structural Formula of Acyclovir



Hydrocortisone, pregn-4-ene-3, 20-dione, 11, 17, 21-trihydroxy-(11(beta))-, is an anti-inflammatory corticosteroid. Its empirical formula is $C_{21}H_{30}O_5$. The structural formula is provided in Figure 2:

Figure 2: Structural Formula of Hydrocortisone



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Acyclovir is an antiviral drug and hydrocortisone an anti-inflammatory drug. [see *Clinical Pharmacology - Microbiology (12.4)*].

12.3 Pharmacokinetics

The plasma concentrations of acyclovir and hydrocortisone were not measured following topical administration of Acyclovir and Hydrocortisone Cream on cold sores.

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin and can have systemic side effects depending on both the potency of the corticosteroid and the surface area of application. Inflammation and/or other disease processes in the skin that disrupt the skin barrier can increase percutaneous absorption.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. They are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

12.4 Microbiology

Mechanism of Action

Acyclovir is a synthetic purine nucleoside analogue with inhibitory activity against herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2) in cell culture and *in vivo*.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In cell culture, acyclovir triphosphate stops replication of herpes viral DNA. This inhibition is accomplished in 3 ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase.

Hydrocortisone is the main glucocorticoid secreted by the adrenal cortex. It is used topically for its anti-inflammatory effects which suppress the clinical manifestations of the disease in a wide range of disorders where inflammation is a prominent feature.

Antiviral Activity

The quantitative relationship between the cell culture susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (EC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays on Vero cells, the median EC_{50} value of acyclovir against clinical herpes virus isolates (subjects receiving placebo) was 1.3 μM (range: < 0.56 to 3.3 μM).

Resistance

Resistance of HSV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV with reduced susceptibility to acyclovir have been recovered from immunocompromised subjects, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated from immunocompromised subjects thus far have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults.

The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Systemic exposure following topical administration of acyclovir is minimal. Results from previous studies of carcinogenesis, mutagenesis and fertility for acyclovir and hydrocortisone are not included in the full prescribing information for Acyclovir and Hydrocortisone Cream due to the minimal exposures that result from dermal application. Information on these studies following systemic exposure is available in the full prescribing information for acyclovir and hydrocortisone products approved for oral or parenteral administration. Dermal carcinogenicity studies have not been conducted.

14 CLINICAL STUDIES

Adults: A double-blind, randomized clinical study involving 1443 subjects with recurrent labial herpes treated with Acyclovir and Hydrocortisone Cream, 5% acyclovir in Acyclovir and Hydrocortisone Cream vehicle or vehicle alone. Subjects had, on average, 5.6 episodes of herpes labialis in the previous 12 months. The median age was 44 years (range 18 to 80 years), 72% were female, and 91% were Caucasian. Subjects were instructed to initiate treatment within 1 hour of noticing signs or symptoms and continue treatment for 5 days, with application of study medication 5 times per day. Ulcerative cold sores occurred in 58% of the subjects treated with Acyclovir and Hydrocortisone Cream compared to 74% in subjects treated with vehicle and 65% in subjects treated with 5% acyclovir in Acyclovir and Hydrocortisone Cream vehicle. The mean time to skin normalization was approximately 1.6 days shorter in the subjects treated with Acyclovir and Hydrocortisone Cream compared to vehicle. Clinical signs in terms of size of the cold sore and symptoms such as tenderness were reduced with Acyclovir and Hydrocortisone Cream as compared to vehicle.
Pediatric Subjects: An open label safety study in adolescents with recurrent herpes labialis was conducted in 134 subjects. Subjects had, on average, 4.0 episodes of herpes labialis in the previous 12 months. The median age was 14 years (range 12 to 17 years); 50% were female and all were Caucasian. Therapy was applied using the same dosing regimen as in adults and subjects were monitored for adverse events and selected efficacy parameters. The safety and efficacy profile appeared similar to that observed in adults.

16 HOW SUPPLIED/STORAGE AND HANDLING

Acyclovir and Hydrocortisone Cream is supplied in plastic-laminated aluminum tubes containing 2 gm or 5 gm of Acyclovir and Hydrocortisone Cream. Each gram of Acyclovir and Hydrocortisone Cream contains 5% (w/w) acyclovir and 1% (w/w) hydrocortisone in an aqueous cream base.
NDC XXXXX-XXX-XXX: 2-gm tubes
NDC XXXXX-XXX-XXX: 5-gm tubes
Store at Controlled Room Temperature [up to 25°C (77°F); excursions permitted to 30°C (86°F). Do not freeze.]

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.1).

17.1 FDA-Approved Patient Labeling

PATIENT INFORMATION
Acyclovir and Hydrocortisone Cream

Acyclovir and Hydrocortisone Cream is for cold sores on lips and around the mouth only. Acyclovir and Hydrocortisone Cream should not be used in eyes, mouth, nose or on genitals.

Read this Patient Information that comes with Acyclovir and Hydrocortisone Cream before you start using it and each time you get a refill. There may be new information. This patient leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is Acyclovir and Hydrocortisone Cream?
Acyclovir and Hydrocortisone Cream is a prescription medicine used in people ages 12 and older to lessen the healing time of cold sores (herpes labialis) and lessen the chance of a cold sore becoming worse (ulcerating). Acyclovir and Hydrocortisone Cream is not a cure for cold sores.
It is not known if Acyclovir and Hydrocortisone Cream is safe or works in children younger than 12 years old.

What should I tell my doctor before using Acyclovir and Hydrocortisone Cream?
Before you use Acyclovir and Hydrocortisone Cream, tell your doctor if you:
- have a weak immune system (become sick very easily). It is not known if Acyclovir and Hydrocortisone Cream will harm you.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if Acyclovir and Hydrocortisone Cream will harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if Acyclovir and Hydrocortisone Cream is passed in your milk to your baby.

How should I use Acyclovir and Hydrocortisone Cream?
- Use Acyclovir and Hydrocortisone Cream exactly as directed by your doctor.
- Use Acyclovir and Hydrocortisone Cream early, at the first sign of a cold sore.
- Wash your hands before and after using Acyclovir and Hydrocortisone Cream.
- Clean and dry the skin before applying Acyclovir and Hydrocortisone Cream.
- Spread a thin layer of Acyclovir and Hydrocortisone Cream on the affected area.
- Do not rub the cold sore because it may spread to other areas around your mouth, or make your cold sore worse.
- Do not cover the cold sore or area around the cold sore with a bandage.
- Do not use other skin products (such as make-up, sun screen or lip balm) or other skin medicine on the cold sore or area around the cold sore.
- Do not bathe, shower or swim until 30 minutes after applying Acyclovir and Hydrocortisone Cream.
- Talk to your doctor if your cold sore is not better in 2 weeks.

What are the possible side effects of Acyclovir and Hydrocortisone Cream?
The most common side effects of Acyclovir and Hydrocortisone Cream are:
- drying or flaking of the skin
- tingling or burning after you apply Acyclovir and Hydrocortisone Cream
- redness of the skin
- changes in your skin color where the cream is applied (pigmentation changes)
- swelling where Acyclovir and Hydrocortisone Cream was applied
- bitter taste after you apply Acyclovir and Hydrocortisone Cream.

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Acyclovir and Hydrocortisone Cream. For more information, ask your doctor or pharmacist.
Call you doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

How should I store Acyclovir and Hydrocortisone Cream?
- Store up to 77°F (25°C); excursions permitted to 86°F (30°C).
- Do not freeze Acyclovir and Hydrocortisone Cream.
- Keep the Acyclovir and Hydrocortisone Cream tube closed tightly.

Keep Acyclovir and Hydrocortisone Cream and all medicines out of the reach of children.

General Information about Acyclovir and Hydrocortisone Cream
Medicines are sometimes prescribed for conditions that are not mentioned in patient leaflets. Do not use Acyclovir and Hydrocortisone Cream for a condition for which it was not prescribed. Do not give Acyclovir and Hydrocortisone Cream to other people, even if they have the same symptoms you have. It may harm them.

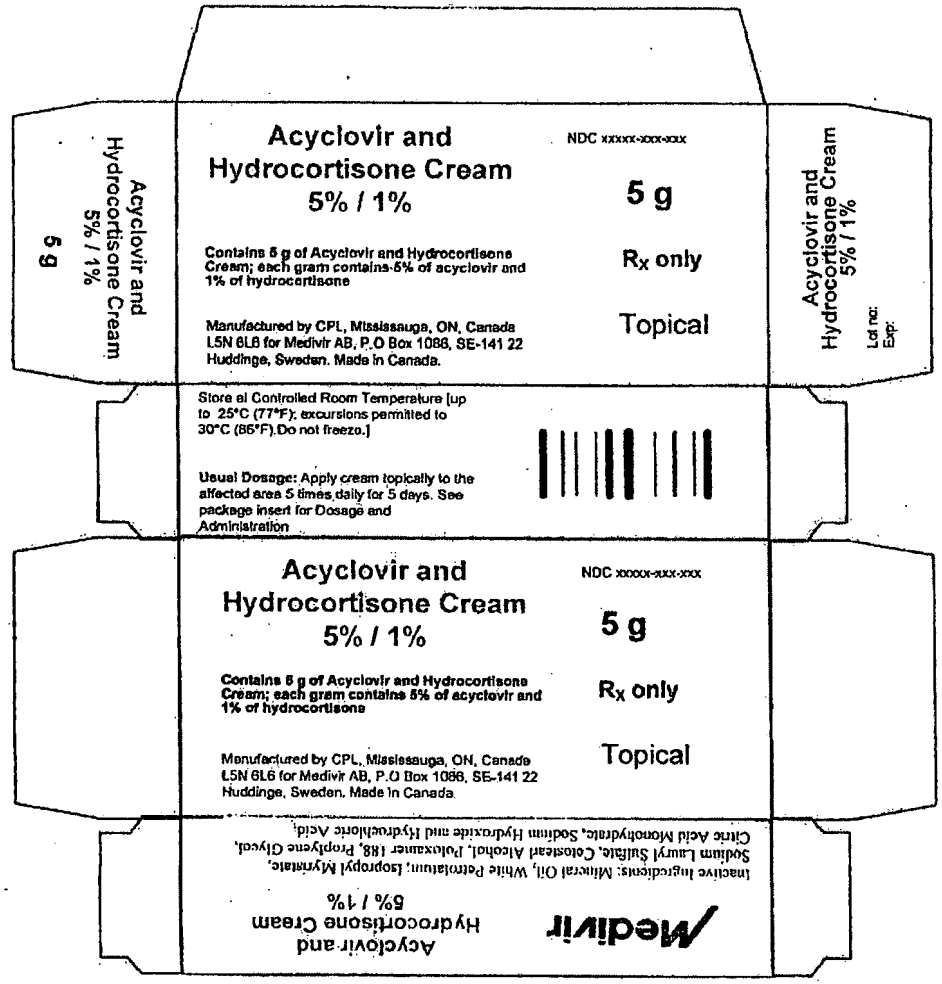
This patient leaflet summarizes the most important information about Acyclovir and Hydrocortisone Cream. If you would like to know more information about Acyclovir and Hydrocortisone Cream, talk with your doctor. You can ask your doctor or pharmacist for additional information about Acyclovir and Hydrocortisone Cream that was written for healthcare professionals.

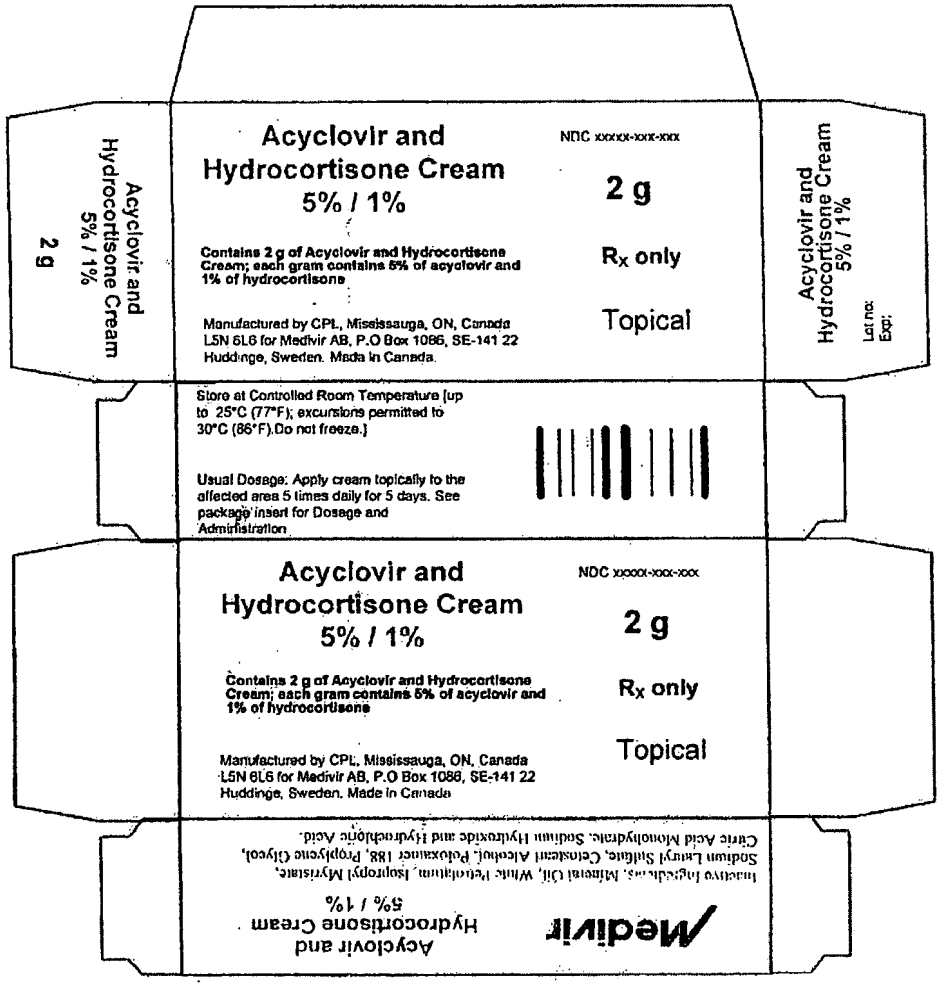
What are the ingredients of Acyclovir and Hydrocortisone Cream?
Active Ingredients: acyclovir and hydrocortisone
Inactive ingredients: cetostearyl alcohol, mineral oil, Poloxamer 188, propylene glycol, isopropyl myristate, sodium lauryl sulfate, white petrolatum, citric acid, sodium hydroxide and water.

Rx Only **Revised: 07/2009**

Manufactured for:
Medivir AB
PO Box 1086
SE-141 22 Huddinge
SWEDEN

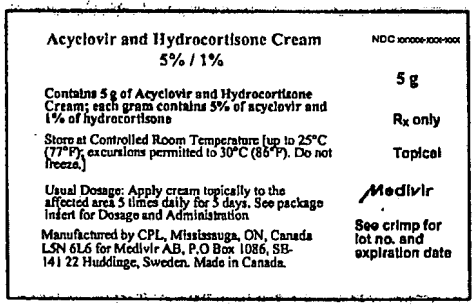
Manufactured by:
Contract Pharmaceuticals Limited
7600 Danbro Crescent
Mississauga, Ontario
CANADA L5N 6L6


Acyclovir and
Hydrocortisone Cream
5% / 1%
5 g
Acyclovir and
Hydrocortisone Cream
5% / 1%
NDC xxxxx-xxx-xxx
5 g
Rx only
Topical
Contains 5 g of Acyclovir and Hydrocortisone Cream; each gram contains 5% of acyclovir and 1% of hydrocortisone
Manufactured by CPL, Mississauga, ON, Canada L5N 6L6 for Medivir AB, P.O Box 1086, SE-141 22 Huddinge, Sweden. Made in Canada.
Acyclovir and
Hydrocortisone Cream
5% / 1%
Lot no:
Exp:
Store at Controlled Room Temperature [up to 25°C (77°F); excursions permitted to 30°C (86°F).Do not freeze.]
Usual Dosage: Apply cream topically to the affected area 5 times daily for 5 days. See package insert for Dosage and Administration
Acyclovir and
Hydrocortisone Cream
5% / 1%
NDC xxxxx-xxx-xxx
5 g
Rx only
Topical
Contains 5 g of Acyclovir and Hydrocortisone Cream; each gram contains 5% of acyclovir and 1% of hydrocortisone
Manufactured by CPL, Mississauga, ON, Canada L5N 6L6 for Medivir AB, P.O Box 1086, SE-141 22 Huddinge, Sweden. Made in Canada.
Medivir
Acyclovir and
Hydrocortisone Cream
5% / 1%
Inactive Ingredients: Mineral Oil, White Petrolatum; Isopropyl Myristate, Sodium Lauryl Sulfate, Cetostearl Alcohol, Poloxamer 188, Propylene Glycol, Citric Acid Monohydrate, Sodium Hydroxide and Hydrochloric Acid.


Acyclovir and Hydrocortisone Cream 5% / 1%
2 g
Acyclovir and Hydrocortisone Cream 5% / 1%
NDC xxxxx-xxx-xxx
2 g
Rx only
Topical
Contains 2 g of Acyclovir and Hydrocortisone Cream; each gram contains 5% of acyclovir and 1% of hydrocortisone
Manufactured by CPL, Mississauga, ON, Canada L5N 6L6 for Medivir AB, P.O Box 1086, SE-141 22 Huddinge, Sweden. Made in Canada.
Acyclovir and Hydrocortisone Cream 5% / 1%
Lot no:
Exp:
Store at Controlled Room Temperature [up to 25°C (77°F); excursions permitted to 30°C (86°F).Do not freeze.]
Usual Dosage: Apply cream topically to the affected area 5 times daily for 5 days. See package insert for Dosage and Administration
Acyclovir and Hydrocortisone Cream 5% / 1%
NDC xxxxx-xxx-xxx
2 g
Rx only
Topical
Contains 2 g of Acyclovir and Hydrocortisone Cream; each gram contains 5% of acyclovir and 1% of hydrocortisone
Manufactured by CPL, Mississauga, ON, Canada L5N 6L6 for Medivir AB, P.O Box 1086, SE-141 22 Huddinge, Sweden. Made in Canada
Medivir
Acyclovir and Hydrocortisone Cream 5% / 1%
Inactive Ingredients: Mineral Oil, White Petrolatum, Isopropyl Myristate, Sodium Lauryl Sulfate, Cetostearil Alcohol, Poloxamer 188, Propylene Glycol, Citric Acid Monohydrate, Sodium Hydroxide and Hydrochloric Acid.

Cream, 5-g Tube

(Actual Size)



(Enlarged View)

Acyclovir and Hydrocortisone Cream
5% / 1%

NDC xxxxx-xxx-xxx

5 g

Contains 5 g of Acyclovir and Hydrocortisone Cream; each gram contains 5% of acyclovir and 1% of hydrocortisone

Rx only

Store at Controlled Room Temperature [up to 25°C (77°F); excursions permitted to 30°C (86°F). Do not freeze.]

Topical

Usual Dosage: Apply cream topically to the affected area 5 times daily for 5 days. See package insert for Dosage and Administration

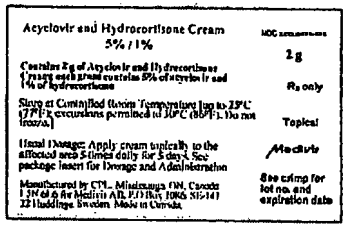
Medivir

Manufactured by CPL, Mississauga, ON, Canada L5N 6L6 for Medivir AB, P.O Box 1086, SE-141 22 Huddinge, Sweden. Made in Canada.

See crimp for lot no. and expiration date

Cream, 2-g Tube

(Actual Size)



(Enlarged View)

Acyclovir and Hydrocortisone Cream 5% / 1%

Contains 2 g of Acyclovir and Hydrocortisone Cream; each gram contains 5% of acyclovir and 1% of hydrocortisone

Store at Controlled Room Temperature [up to 25°C (77°F); excursions permitted to 30°C (86°F). Do not freeze.]

Usual Dosage: Apply cream topically to the affected area 5 times daily for 5 days. See package insert for Dosage and Administration

Manufactured by CPL, Mississauga, ON, Canada L5N 6L6 for Medivir AB, P.O Box 1086, SE-141 22 Huddinge, Sweden. Made in Canada.

NDC xxxxx-xxx-xxx

2 g

R_x only

Topical

Medivir

See crimp for lot no. and expiration date

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/s/

JEFFREY S MURRAY
07/31/2009

EXHIBIT 6 1st page

US006068860A

United States Patent [19]

Carlsson et al.

[11] **Patent Number: 6,068,860**

[45] **Date of Patent: May 30, 2000**

[54] **PHARMACEUTICAL FORMULATION**

[75] Inventors: **Anders Nils-Erik Carlsson**; **Johan Georg Harmenberg**; **Bengt Göran Herslöf**, all of Stockholm; **Ann Harriet Margareta Kristofferson**, Södertälje; **Stefan Karl Lundquist**, Skärholmen, all of Sweden

[73] Assignee: **Astra Aktiebolag**, Sodertalje, Sweden

[21] Appl. No.: **08/602,784**

[22] PCT Filed: **Feb. 2, 1996**

[86] PCT No.: **PCT/SE96/00123**

§ 371 Date: **Mar. 8, 1996**

§ 102(e) Date: **Mar. 8, 1996**

[87] PCT Pub. No.: **WO96/24359**

PCT Pub. Date: **Aug. 15, 1996**

[30] **Foreign Application Priority Data**

Feb. 6, 1995 [WO] WIPO PCT/SE95/00112

[51] **Int. Cl.**[7] **A01N 59/26**

[52] **U.S. Cl.** **424/601**; 514/178

[58] **Field of Search** 424/601; 514/178

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,512,978	4/1985	Inwood	424/145
4,610,868	9/1986	Fountain et al.	424/1.1
5,227,165	7/1993	Domb et al.	424/450

FOREIGN PATENT DOCUMENTS

636255	4/1993	Australia .
0009842	4/1980	European Pat. Off. .
9842	4/1980	European Pat. Off. .
0249561	12/1987	European Pat. Off. .
0350287	1/1990	European Pat. Off. .
8905152	6/1989	WIPO .
9503805	9/1995	WIPO .

OTHER PUBLICATIONS

The Merk Index, 10th Edition, p. 607, entry 4135, Apr. 24, 1984.

Jocam, U.E.; Load—Liposomen topisch appliziert, Pharmaceutische Zeitung Nr. 33, Aug. 13, 1992.

Schreier, H.; Liposomes and iosomes as topical drug carriers: dermal and transdermal drug delivery, Journal of Controlled Release 30 (1994), 1–15.

Spruance, S.L.; Topical therapy of Mucocutaneous Herpesvirus Infections, International Antiviral News, Jun. 1994.

Alenius, S, et al; Therapeutic Effects of Foscarnet Sodium and Acyclovir on Cutaneous Infections Due Herpes Simplex Virus Type 1 in Guinea Pigs, J. Inf. Dis. 1982, vol. 145, No. 4, Apr. 1982.

The Human Herpesviruses, ed. Roizman et al. 1993, Whitely Richard et al.; The Epidemiology and Clinical Manifestations of Herpes Simplex Virus Infections.

(List continued on next page.)

Primary Examiner—Dwayne C. Jones
Attorney, Agent, or Firm—White & Case L.L.P.

[57] **ABSTRACT**

The invention relates to a pharmaceutical composition for topical administration comprising a combination of foscarnet and an antiinflammatory glucocorticoid, in admixture with a carrier based on galactolipids and a polar solvent. The pharmaceutical composition can be used in a prophylactic and/or curative treatment of herpesvirus infections in mammals including man.

The invention also relates to the use of said pharmaceutical composition in the manufacture of a medicament for said prophylactic or curative treatment.

16 Claims, 3 Drawing Sheets

EXHIBIT 7

1103326-0202

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Harmenberg, et al.
Serial No.	:	08/612,847
Filed	:	March 8, 1996
For	:	NOVEL PHARMACEUTICAL COMBINATION

TERMINAL DISCLAIMER

The owner, Astra Aktiebolag, of 100% interest in the instant application hereby through its undersigned agent, who is empowered to act on behalf of Astra Aktiebolag, disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. §§154-156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 6,068,860. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application which would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §§154-156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in

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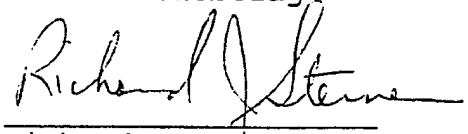
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: October 6, 2000

Respectfully submitted,

Astra Aktiebolag



Richard J. Sterner
Reg. No. 35,372

Applicants' Agent
Customer Number 007470
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Agent's Direct Line:
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PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
RE39,264	$2,480.00	$0.00	06/15/09	10/771,259	01/08/02	03/08/96	08	NO	1718-0214P

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Patent Bibliographic Data					09/15/2009 02:20 PM
Patent Number:	RE39264		**Application Number:**	10771259	
Issue Date:	09/05/2006		**Filing Date:**	03/08/1996	
Title:	PHARMACEUTICAL COMBINATION				
Status:	12th year fee window opens: 01/08/2013			**Entity:**	Large
Window Opens:	01/08/2013	**Surcharge Date:**	07/09/2013	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:	1553	MAINTENANCE FEE DUE AT 11.5 YEARS			
Surcharge Fee Code:					
Most recent events (up to 7):	06/15/2009	Payment of Maintenance Fee, 8th Year, Large Entity. --- End of Maintenance History ---			
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EXHIBIT 9

Antiviral Chemistry & Chemotherapy 14:205–215

ME-609: a treatment for recurrent herpes simplex virus infections

Johan G Harmenberg[1,2]*, Aftab R Awan[3†], Stefan Alenius[4], Lars Ståhle[5], Anna C Erlandsson[6], Gunilla Lekare[7], Ola Flink[8], Elisabeth Augustsson[1], Torbjörn Larsson[1], Ann-Charlotte Wikström[6], Pontus Stierna[9], Hugh J Field[3], Alf G Larsson[8] and Bo Öberg[1,2]

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[2]Karolinska Institutet, Stockholm, Sweden
[3]Centre for Veterinary Science, University of Cambridge, Cambridge, UK
[4]National Veterinary Institute, Uppsala, Sweden
[5]Department of Clinical Pharmacology, Karolinska Institutet, Huddinge University Hospital, Huddinge, Sweden
[6]Department of Medical Nutrition, Karolinska Institutet, Huddinge, Sweden
[7]CCS AB, Borlänge, Sweden
[8]AstraZeneca, Södertälje, Sweden
[9]Department of Clinical Science, Huddinge University Hospital, Huddinge, Sweden

*Corresponding author: Tel: +46 8 608 31 00; Fax: +46 8 608 31 99; E-mail: johan.harmenberg@medivir.se
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Studies in conventional murine models of HSV infection use immunologically naive animals. These models thus mimic primary infections rather than recurrent infections in humans. We have, therefore, used a newly developed mouse model that more closely mimics recurrent HSV infection in humans. In this model, the mice are infected, and zosteriform HSV-1 infection develops in the presence of a primed immune response using adoptive transfer of immunity (ATI) as we have described previously. Using the ATI mouse model, it has been shown that a more beneficial therapy for recurrent mucocutaneous HSV infection could be achieved by controlling both the viral replication and the inflammatory response to the virus. Topical treatment was initiated in this model at the time of first occurrence of symptoms and was given three times daily for 4 days. Topical treatment with ME-609 (which contains 5% acyclovir and 1% hydrocortisone) in the ATI mouse model was substantially more efficacious than 5% Zovirax® cream, 1% hydrocortisone or no treatment, respectively. The beneficial properties of ME-609 were also found to be superior to those of Zovirax® cream when tested in the standard guinea pig model, representing a primary HSV infection. ME-609 represents a novel treatment principle of recurrent HSV infections and the present paper summarizes the preclinical and early clinical experience of ME-609.

Key words: HSV-1, animal models, acyclovir, hydrocortisone, immune response.

Introduction

Primary infection with herpes simplex virus (HSV) usually occurs as a labial infection in childhood or as a genital infection in early adulthood, and is characterized by viral replication usually lasting approximately 10–14 days. The immune response is not fully developed until at least 7 days after infection. The lesions heal soon after the virus is cleared by the immune response (Alenius *et al.*, 1982; Spruance *et al.*, 1977, Spruance, 1992). Since healing of the lesions is a result of viral clearance, treatment with antiviral drugs is able to shorten the clinical episode by curtailing viral replication faster. Thus, treatment of primary genital HSV infections with oral or intravenous administration of antiviral drugs, such as acyclovir, reduces the period of viral shedding and gives a significant improvement in clinical parameters such as pain and time to healing (Richards *et al.*, 1983). This pattern of extended viral replication that resolves as the immune response develops is also shown in traditional animal models of primary HSV infection, such as primary cutaneous infection of guinea pigs with HSV (Alenius *et al.*, 1982). In such animal models of primary HSV infection, treatment with antiviral drugs substantially reduces the duration of viral replication and thus the clinical episode (Alenius *et al.*, 1982; McKeough & Spruance, 2001; Poli *et al.*, 2001).

During primary infection, the virus enters the nerve endings and is transported in the axons towards the

ganglion, where the virus remains latent within the ganglionic neurons for the rest of the individual's life. At a later date, the virus may be reactivated and may travel back down the nerve to the skin, where it replicates producing a clinical episode of reactivated HSV infection. The recurrent disease differs from the primary episode in that the virus is typically cleared much more rapidly (within 3 days or less) due to the immediate immune response, which is already primed after previous episodes (Spruance *et al.*, 1977; Spruance, 1992). However, although in recurrent infection the immune response is much quicker and more effective, it is also the cause of most of the clinical symptoms of pain, redness, swelling and tenderness, through the inflammatory response to the virus. There is strong evidence that cell-mediated immune responses contribute significantly to the tissue damage and lesion development associated with HSV infection. Thus, although the virus is cleared more rapidly, the symptoms usually remain for about a week after the time at which virus can no longer be isolated, and the lesion typically takes 7–10 days to heal (Spruance, 1992; Spruance *et al.*, 1977). Consequently, treatment of recurrent HSV infection with exclusively antiviral drugs has little effect on the clinical parameters of disease, even though the duration of viral shedding may be shortened (Corey *et al.*, 1982a,b; Raborn *et al.*, 2002; Reichman *et al.*, 1983; Spruance & Crumpacker, 1982; Spruance *et al.*, 2002; Spruance *et al.*, 1997).

The characteristics of recurrent HSV infection, i.e. short period of viral replication and excessive inflammatory response to the virus, are not reflected in presently available animal models. We have, therefore, developed a new animal model, the adoptive transfer of immunity (ATI) mouse model, of HSV infection using zosteriform spread of virus in combination with ATI. This model mimics both the clinical parameters of reactivated HSV infection and the effects of antiviral treatment (Awan *et al.*, 1998 a,b). Using this model, we have developed a new approach for the treatment of recurrent HSV infection in that both viral replication is curtailed and the inflammatory response controlled. This is achieved by combining an antiviral compound with an agent with immunomodulatory properties in a topical formulation. Such a topical combination would have the dual properties of both inhibiting viral replication and controlling the inflammatory response and promoting healing. A topical formulation of 5% acyclovir and 1% hydrocortisone (ME-609), aiming to have these properties, has been developed by Medivir AB and AstraZeneca.

We have evaluated this new concept in cell culture experiments, skin penetration experiments and animal models of primary HSV infection as well as in our new ATI mouse model, which mimics recurrent HSV infections. Recently, Phase I and II clinical studies have been performed that confirm the ability of the ATI mouse model to predict efficacy against recurrent HSV disease (Evans *et al.*, 2002).

Materials and methods

Cell culture studies

Cells and virus. Human embryonic lung (HEL) fibroblasts (kindly provided by the Swedish Institute for Infectious Disease Control, Solna, Sweden) and African green monkey kidney (Vero) cells (ATCC, Rockville, Maryland, USA) were propagated in Earl's Modified Eagle's Medium (GibcoBRL Laboratories, Inc., Gaithersburg, Md., USA) supplemented with 10% foetal bovine serum (Sigma Chemical Co., St. Louis, MO, USA), 2 mM L-glutamine, 100 μg/ml streptomycin and 100 U/ml penicillin at 37°C in 5% CO_2. The C42 P2 strain of HSV-1 (a clinical isolate obtained from the Swedish Institute for Infectious Disease Control, Solna, Sweden) was grown and titrated in Vero cells by plaque assay.

HSV-1 (strain SC16) was originally isolated from a clinical case of herpes labialis (Hill *et al.*, 1975). Virus was grown in baby hamster kidney cells (BHK-21) following established procedures (Field *et al.*, 1995) and stored at −70°C.

Cell culture procedure. HEL fibroblasts (4×10^5 cells) were seeded into 12-well plates and grown for 3 days at 37°C in 5% CO_2. Confluent cells were inoculated with the C42 p2 strain of HSV-1 in serum-free medium at a multiplicity of infection of 0.001. After 45 min of adsorption at 37°C in 5% CO_2, serum supplemented medium containing acyclovir in the range of 0–10 μM in combination with hydrocortisone in the range of 0–100 μM was added. Cells were incubated for an additional 48 h at 37°C in 5% CO_2 and then supernatants were removed and frozen at −80°C.

Vero cells (2×10^5 cells) were plated and grown in 24-well plates. At confluency, cells were infected with the viral supernatants eluted in serum-free medium in series of dilutions from 10^{-2} and to 10^{-6}. After 1 h of adsorption fresh medium supplemented with 10% foetal bovine serum and 2 mg/ml human immunoglobulins (Beriglobin, Centeon Pharma GmBh, Marburg, Germany) was added. The infection proceeded for 3 days at 37°C in 5% CO_2, after which cells were stained with crystal violet and plaques were counted. The result was shown as plaque forming units (PFU)/ml.

Formulations

ME-609 is a cream formulation containing 5% acyclovir and 1% hydrocortisone. All excipients are well-known and widely used in topical products. All formulations were prepared at CCS AB, Borlänge, Sweden. Commercially

available Zovirax® cream, containing 5% acyclovir, was repacked to preserve blinding whenever appropriate. Commercially available 1% hydrocortisone cream was obtained from CCS AB, Borlänge, Sweden.

Guinea pig experiments

The backs of the Dunkin-Harley guinea pigs were plucked, shaved and depilated with Opilca® (GlaxoSmithKline Consumer Healthcare, Copenhagen, Denmark) as previously described (Alenius & Oberg, 1978). Twenty microlitres of HSV-1 strain C42 (10^6 PFU/ml) was applied to four areas on each animal on day 0 using a spring-loaded vaccination instrument according to previously described procedures (Hubler *et al.*, 1974). Two areas on each animal were treated with topical placebo and served as controls. The other two areas were treated with different topical formulations containing antiviral compounds. Treatment was started at 24 or 48 h after infection depending on experimental design (see figure legends for details) and continued for 3 or 4 days. All non-commercial formulations containing active ingredients used in the experiments were blinded to the investigator. In a subsequent experiment (Figure 1b), commercially available Zovirax® cream was repacked into similar tubes by third party and the study was thus blinded. The inoculated areas were assessed for clinical signs of HSV lesions once daily throughout the experiments until healing. All scoring was performed in a blinded fashion (Table 1). The score system was adopted from previously published procedures (Alenius & Oberg, 1978).

ATI mouse model

The model itself and some results using the model have previously been published (Awan *et al.*, 1998a,b).

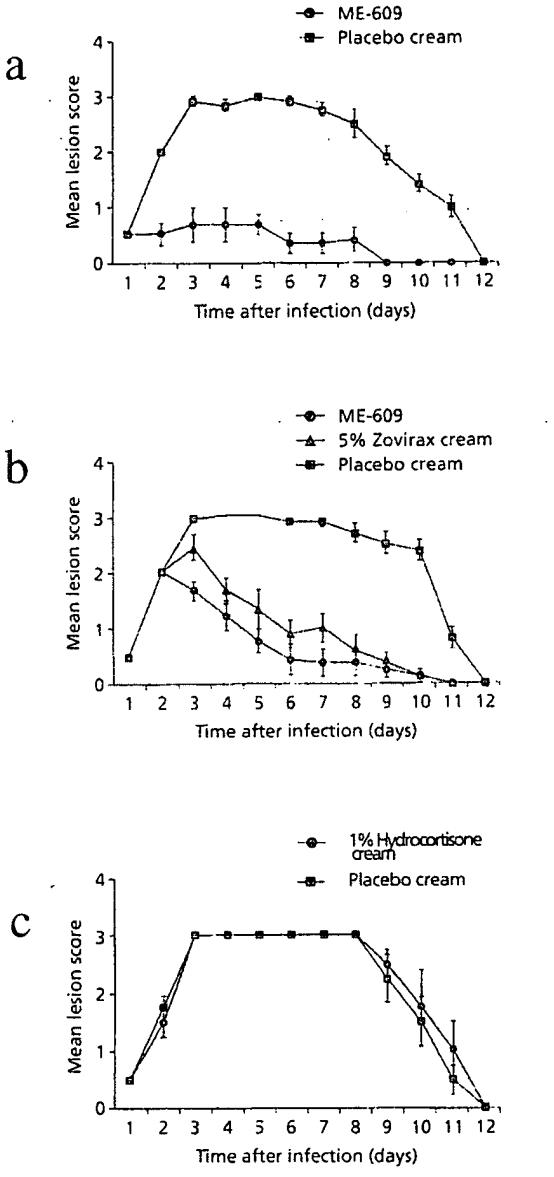
Inoculation of mice

Inoculation was performed as previously described (Blyth *et al.*, 1984). Briefly virus suspension (2×10^5 PFU) was placed on the skin of female Balb/C mice, weighing 16–18 g, on the right side of the ventral surface of the neck, then 8–10 superficial light strokes were made by a hypodermic needle in a criss-cross pattern to produce the scarification.

Adoptive transfer of immunity (ATI). A group of immune donors were prepared by inoculation of HSV-1 (10^5 PFU) into the skin of both left and right ears of female Balb/C mice. The cervical lymph nodes were removed at 7 days after infection and a suspension of lymph node cells was prepared. Recipient mice were given 3.6×10^6 live immune cells via the coccygeal vein. The recipient mice had been infected 2 days previously with HSV-1 by neck scarification (see above).

Experimental design. The animals were divided into three treatment groups and one untreated control group.

Figure 1. Effect of ME-609 on lesion score in a primary HSV-1 infection in guinea pigs



Three or four areas on six to nine guinea pigs were infected on day 0 with HSV-1, as described in 'Materials and methods'. One area on each animal was treated topically with ME-609 from day 1 (Figure 1a and 1c) or day 2 (Figure 1b) for 4 days. One area on each animal was treated with 5% Zovirax® cream while the remaining two areas were treated with placebo. Treatments were applied twice daily (Figure 1a) or four times daily (Figure 1b) for 4 days. The lesion score was assessed daily until healing. The average lesions score and standard error of each day is shown. The effect of 1% hydrocortisone cream applied twice daily for 3 days was compared with placebo in eight areas using similar procedure (Figure 1c). Statistical analysis showed that ME-609 treatment resulted in significant improvement over placebo in both Figure 1a (P=0.014) and Figure 1b (P<0.001) study settings. The difference between ME-609 and 5% Zovirax® treatment (Figure 1b) was not statistically significant.

Table 1. Lesion scoring system

Lesion score	Appearance of inoculated skin
0.5	Erythematous and slightly oedematous
1	Erythema and one or two small vesicles
2	Erythema and numerous small vesicles
3	Numerous large vesicles; if in close juxtaposition, coalesced
3	Vesicles dried, large crusts
2	Circa 50% crusts fallen off
1	Circa 10% of the crusts remaining
0	Uninfected or healed area, no crusts or vesicles; trauma from inoculation or traces from infection can be present

All of these animals were given ATI. Each study group consisted of 10 animals for observation (zoster score and ear thickness increase). In addition, 16 animals were included in each group for titration of virus. Four animals were sacrificed for virus titration on days 5, 7, 9 and 13 post infection (p.i.), respectively.

Application of study creams. The ear pinnae of the mice were treated topically with study creams three times a day at 8 h intervals i.e. 08:00, 16:00 and midnight. The topical treatment was started on day 4 at 08:00 p.i. and continued to day 7 at midnight p.i. All creams were packed in identical containers and coded and the study was thus blinded.

Clinical disease assessments. The thickness of the ear pinna, ipsilateral to the infection, was measured daily using an Engineers' micrometer (Field *et al.*, 1979). The development of lesions with respect to zoster score on the neck (primary site) and pinna (zosteriform spread) was monitored visually using a magnifying glass. The zosteriform lesions were scored according to a scale previously described (Nagafuchi *et al.*, 1979). The following zoster scores were used; 0 unchanged ear, 1 isolated zosteriform lesions, 2–4 describe the ulceration of confluent zosteriform lesions from mild to severe.

Virus titration. At various times, mice were euthanized and each mouse's ear ipsilateral to the infection site was removed and homogenized. Following topical treatment, there is a possibility that the antiviral drug may be present on the ear samples obtained and this may affect the virus isolation. The skin was, therefore, thoroughly washed before homogenization and virus titration. The theoretical maximum concentration of acyclovir in the titration was then not high enough to affect the plaque counts. As a further precaution, 50 μM of thymidine was added to the growth medium to decrease any possible remaining antiviral activity of acyclovir. Acyclovir is activated by phosphorylation by virus specific thymidine kinase and addition of thymidine to the growth medium blocks activation of any remaining acyclovir (Harmenberg, 1983). Virus was titred as previously described (Field *et al.*, 1995).

In vitro skin penetration

The backs of the Dunkin-Harley guinea pigs were plucked, shaved and depilated with Opilca® as previously described (Alenius & Oberg, 1978). Two days after depilation the animals were sacrificed and full thickness skin was removed and frozen in −70°C.

The subcutaneous fat was removed by blunt dissection and the skin samples were applied to a two-chamber diffusion cells system as previously described (Aulton, 1988). The upper chamber was open to facilitate cream application to the skin surface (surface area 0.93 cm^2). Both formulations studied in the experiment were blinded. The receiving chamber contained Ringer solution and samples were taken at various times following application of creams to the skin surface.

The acyclovir content of the samples from the receiving chamber was analysed by HPLC with UV-detection using a mobile phase of 0.05 M $(NH_4)H_2PO_4$ buffer at pH 7.00 and 15% methanol. The column used was a 150×2.1 mm C18 Zorbax 5 μm particle size reversed phase column. The mobile phase was delivered at 0.2 ml/min and detection was at 254 nm. The retention time of acyclovir in this system was approximately 2.7 min.

Statistical methods

Statistical analyses used for comparisons between treatments (ear thickness and zoster score using the ATI mouse model) were based on Kruskal–Wallis for testing all treatments against each other. A significant *P*-value indicated that at least one treatment differs systematically from the others, and was thus followed by *post hoc* pair wise comparisons using the Mann–Whitney U test. In the analyses of the zoster score, the individually observed difference between day 4 and day 9 was known since all observations at day 4 were equal to 0. For the analysis of ear thickness, the observations were dependent but not individually identified. The number of degrees of freedom was still limited to the number of independent observations (Altman, 1991).

The viral growth (log transformed) in the cell studies was evaluated by a one way ANOVA for each of the ACV concentrations 0, 0.1 and 1 μM. An overall significant result was followed by *post hoc* ANOVA multiple comparisons.

An overall ANOVA with both ACV and HC included as factors was not feasible due to an uncontrollable heterogeneity of the variance structure.

The cumulative scores, which were proportional to a possible area under the curve, in the guinea pig

experiments were used for comparison between treatments. The analysis was made conservative by considering the most positive result of the two placebo scores. As all guinea pigs have all treatments the Friedman ANOVA for ranks was used, followed by *post hoc* tests using Friedman multiple comparisons for ranks.

In vitro skin penetrations profiles: ME-609 was compared with 5% acyclovir cream by first estimating the intensity over time for each guinea pig (the slope after linearization of the process). The mean intensities for the two groups were then compared using a t-test (the estimated intensities were found to reasonably follow a normal distribution).

The virus titres (log transformed) for untreated and 1% hydrocortisone cream-treated mice were compared over time (5, 7, 9 and 13 days) using a two factor Mixed Model ANOVA with substance and time as factors and mouse as replicates with substance and time. The Mixed Model analysis was used due to a non-homogenous variance structure over time.

Results

Cell culture studies

After infection with the clinical HSV-1 isolate C42 p2, HEL cells were treated for 48 h with 0–10 μM acyclovir in the presence of 0–100 μM hydrocortisone (Figure 2). Treatment with acyclovir significantly ($P<0.001$) inhibited viral multiplication in accordance with previous experience (Harmenberg *et al.*, 1980). The addition of hydrocortisone (up to 100 μM) did not alter the inhibition by acyclovir *in vitro*. Statistical analysis showed that hydrocortisone treatment alone in the range of 0.1–100 μM did not influence the viral growth.

Guinea pig experiments

The antiviral activity of ME-609 was tested using the primary HSV-1 infection guinea pig model. Animals treated with placebo formulation developed skin lesions within 2 days of infection. The lesions healed around day 10–12 p.i. ME-609 showed a pronounced beneficial effect in this model both when treatment was initiated 24 hours and 48 h after infection (Figure 1a, $P=0.014$ and 1b, $P<0.001$). The average lesion score was below 1 at all times when treatment was initiated at 24 h and most areas were only erythematous and slightly oedematous. The lesion development was thus interrupted by ME-609 treatment.

When treatment was delayed to 48 h after infection to assess the effect on developed lesions, treatment with ME-609 was at least as effective as treatment with 5% Zovirax® cream even though superiority could not be shown with statistical methods (Figure 1b). The comparison between ME-609 and Zovirax® cream was performed in repeated experiments with similar results. ME-609 tended to be superior at all times tested (data not shown). Commercially available 1% hydrocortisone cream did not, as expected, reduce lesion score in this model (Figure 1c). However, the small size of the data set precluded statistical analysis.

Virus titres in the skin of the animals were assessed at the peak of the virus infection (day 5) and immediately after the viral shedding period. Similar low virus titres were obtained from Zovirax® cream and ME-609-treated areas (data not shown). No prolongation of the viral shedding period was seen. Furthermore, all treatments were safe and no treatment-related adverse effects were noted.

ATI mouse model experiments

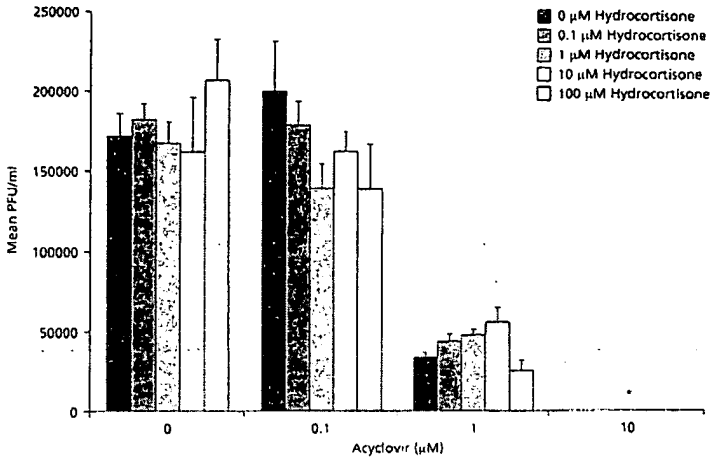
Ear thickness increase and zoster score. Treatment with topical ME-609 showed beneficial effects in terms of both ear thickness increase and zoster score (Tables 2 and 3). Furthermore, the results indicated that ME-609 treatment was more effective than the other treatments. Two different parameters were calculated: the average of the zoster score and ear thickness increase on day 9 p.i. and the average cumulative zoster score and ear thickness increase. Day 9 p.i. was selected as an appropriate time when full effect of the different treatments was expected. Day 9 p.i. is also a time when the clinical signs (ear thickness increase and

Table 2. Effects of different treatments on ear thickness increase using the ATI mouse model

	Average increase in ear thickness±SE (mm)*	% of control	Average day 4–15 increase in cumulative ear thickness (mm)†	% of control
ME-609	0.15 ±0.03‡	34%	1.04	14%
Zovirax® cream	0.48 ±0.08	110%	3.99	100%
1% hydrocortisone cream	0.23 ±0.03	52%	2.74	69%
Untreated control	0.43 ±0.05		3.99	

* Average day 9 p.i. increase in ear thickness (mm) compared with day 4 baseline.
† Increases from day 4 p.i. (baseline) calculated for day 4–10, 12, 13 and 15 p.i. In addition, intrapolated values from day 11 and 14 p.i. The mice were not individually marked and standard error could therefore not be obtained.
‡The ME-609-treated group was significantly better than the untreated control group ($P<0.001$), the 1% hydrocortisone cream-treated group ($P<0.04$) and the 5% Zovirax® cream group ($P<0.001$).

Figure 2. Effects of acyclovir and hydrocortisone on HSV-1 replication in HEL cells



Viral multiplication in HSV-1-infected HEL cells treated with a combination of increasing concentrations of acyclovir and hydrocortisone. Cells were infected at a multiplicity of infection of 0.001 and, after 45 min of absorption, fresh medium containing acyclovir and hydrocortisone was added. The infection proceeded for 48 h and then viral supernatants were frozen at –80°C before being titrated in Vero cells. Results shown as average with standard error. Statistical analysis showed that hydrocortisone treatment alone in the range of 0.1–100 µM of hydrocortisone did not influence the viral growth. *no virus detectable in any group

Table 3. Effects of different treatments on zoster score using the ATI mouse model

	Average zoster score ±SE at day 9 p.i.	% of control	Average cumulative zoster score	% of control (day 4–15 p.i.)*
ME-609	2.0±0.2†	58%	15.3	60%
Zovirax® cream	2.4±0.3	70%	19.1	75%
1% hydrocortisone cream	2.8±0.2	80%	23.6	93%
Untreated control	3.4±0.3		25.3	

* Measurements summated for day 4–10, 12, 13 and 15 p.i. In addition, intrapolated values from day 11 and 14 p.i. The mice were not individually marked and standard error could therefore not be obtained.
† The ME-609 group was significantly better than the untreated control group ($P<0.001$), the 1% hydrocortisone group ($P<0.01$) while the difference from the 5% Zovirax® cream group was not statistically significant.

zoster score) are approaching their peak values. For ear thickness increase, the increase in value over day 4 p.i. (baseline value) was used in the calculations. The average cumulative zoster score and ear thickness increase as calculated in Tables 2 and 3 were used as the second parameter. Here again, the changes over baseline were used for the ear thickness increase calculations.

ME-609 was shown to improve both the day 9 p.i. ear thickness increase and the average cumulative ear thickness increase by 66% ($P<0.001$) and 86% in comparison to untreated control mice. Similarly, the average day 9 p.i. zoster score and the average cumulative zoster score were improved by ME-609 treatment by 42% ($P<0.001$) and 40% in comparison with untreated control mice, respectively. The ME-609 treatment was more efficacious than treatment with Zovirax® cream ($P<0.001$) or 1% hydrocortisone cream ($P<0.04$) with respect to ear thickness increase. ME-609 treatment was better than hydrocortisone cream treatment with respect to zoster score ($P=0.01$), while the improvement vs. Zovirax® cream did not reach statistical significance in the present experiment.

Zovirax® cream did not show any effect on ear thickness increase. When measuring zoster score, Zovirax® cream showed a relatively good effect in comparison with untreated control animals (Tables 2 and 3). This effect was greater than previously seen in the ATI mouse model (unpublished data).

Hydrocortisone cream showed a substantial effect on ear thickness increase, as expected, while the effect on zoster score was limited (Tables 2 and 3). The variability (mea-

sured as standard error) of the results in the ATI mouse model at time points after the peak of infection is however substantial.

Virology data

Groups of four mice were euthanized on days 5, 7, 9 and 13 after infection and the virus titres of the ears were assessed by plaque assay. The results showed that both ME-609 and Zovirax® cream reduced the virus titres over time compared with untreated control mice at all time points in a similar fashion (Figure 3). Hydrocortisone treatment increased the viral shedding over time compared with the untreated control group (P=0.04) and low but measurable virus titres were also found on day 13 p.i.

Skin penetration

ME-609 and a 5% acyclovir cream formulation, similar to Zovirax® cream, were tested on full thickness guinea pig skin (n=7–8). In this experiment, application of ME-609 reached higher acyclovir concentrations in the receiving chamber than 5% acyclovir cream (Figure 4, P=0.0004).

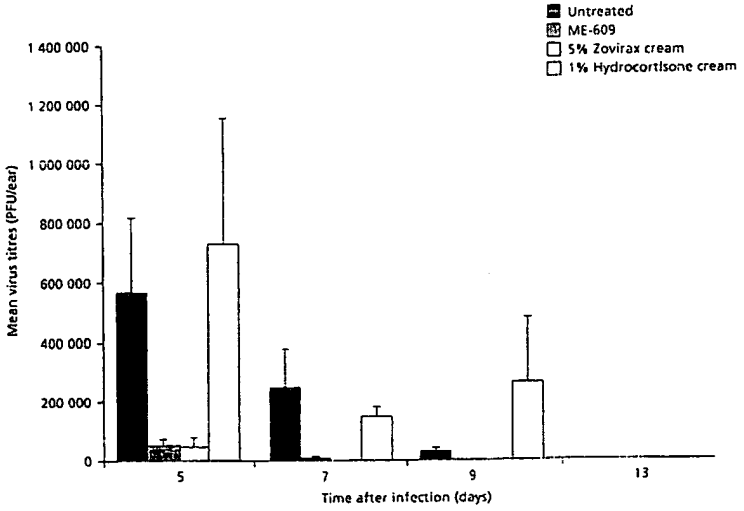
Discussion

As stated in the introduction, primary infection models fail to mimic the clinical situation with respect to recurrent HSV infections. The ATI mouse model offers the possibility of representing the immunological as well as the virological pattern associated with recurrent HSV infections in man. The ATI mouse model is, however, labour-intensive and cumbersome to use. In addition, it is a complex model with many different parameters that can contribute to experimental variation. It is, therefore, critical that all treatments and assessments are performed blinded as in the present study. The ATI mouse model can be used to assess proof-of-principle but it would be difficult to perform detailed assessments, for example dosing or dosing intervals. In addition, mice will lick their ears and oral exposure to the topical drugs cannot be excluded, even though a small amount of treatment is applied and the gastrointestinal uptake of acyclovir and hydrocortisone is limited. Finally, mice will scratch their infected ears, which could worsen the symptoms and increase experimental variation. This is especially true in the untreated groups or the groups receiving suboptimal treatment and at later time points, after the peak of infection.

Three parameters were used to assess the effectiveness of different formulations in the ATI mouse model. Zoster score is the traditional way to determine clinical progression of herpetic lesions in rodents. It is however a subjective parameter dependent on the experience of the investigator. The immune response and the subsequent inflammation induced by the virus infection of mouse ears cause increased ear thickness, a parameter that can readily be objectively measured by mechanical means. Virus titrations of the tissues also provide quantitative information.

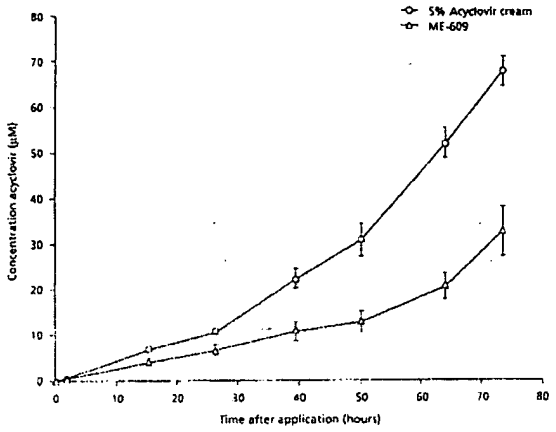
Previous experience with the ATI mouse model has been summarized in two published articles (Awan *et al.*, 1998a,b). We initially used the ATI mouse model to study antivirals in combination with a large number of substances

Figure 3. Viral titres in ATI mice infected with HSV-1 and given topical treatments



Mean virus titres and standard error in mouse ears measured at various times after infection. Groups of four animals were sacrificed at day 5, 7, 9 and 13 after infection. The virus titres of the ears were assessed as described in 'Materials and methods'. The virus titres were below the limits of detection (<20 PFU/ear) in the 5% Zovirax® group on day 7 and in both the ME-609 and the 5% Zovirax® group on day 9. On day 13 all groups were below the limits of detection except the 1% hydrocortisone cream group, which showed a mean virus titre of 100 PFU/ear. The hydrocortisone treated group showed statistically increased viral shedding over time compared with the untreated control group (P=0.04).

Figure 4. Penetration of acyclovir through guinea pig skin from topical ME-609 and acyclovir cream



Acyclovir penetration profiles of ME-609 and 5% acyclovir cream applied topically to full thickness guinea pig skin. ME-609 was applied to eight skin samples at time 0. Acyclovir cream was applied to seven skin samples. The concentration of acyclovir in the receiving chamber was measured at various time points shown as average with standard error. Application of ME-609 resulted in significantly higher acyclovir concentrations in the receiving chamber over time compared with 5% acyclovir cream treatment (P=0.0004).

with immunomodulatory properties including, e.g. glucocorticosteroids, non-steroidal anti-inflammatory drugs and local anaesthetics (unpublished). Combinations of antivirals with glucocorticosteroids were shown to be more beneficial than other combinations. We also found that the combination of antiviral drugs with hydrocortisone was more effective than combinations with other glucocorticosteroids (unpublished).

The most important result of the present study is the demonstration that the combination of antiviral compounds (in this case, acyclovir) with a mild immunomodulatory agent (hydrocortisone) is clearly beneficial with respect to the measured parameters. The control groups (acyclovir alone, hydrocortisone alone and untreated infected mice) all showed less effect on the measured parameters than the ME-609 treated group. As expected, the mice treated with Zovirax® cream did not show any beneficial effect with respect to ear thickness increase. However, the result suggested that Zovirax® cream had a somewhat better effect on zoster score than could be expected based on previous experience with foscarnet (Awan *et al.*, 1998a) and acyclovir (unpublished data). This could be explained by experimental variation as discussed above or by the fact that only 3.6×10^6 live immune cells were given as ATI to recipient mice in the present experiment which was less than the intended target of $1–2\times10^7$ cells. Both ME-609 and Zovirax® cream treatment reduced the virus titres compared to untreated control mice.

Hydrocortisone cream treatment had a good effect on ear thickness increase during the treatment period (days 4–7 p.i.). After the treatment period, the effect of hydrocortisone used alone was less pronounced compared to ME-609 treatment. Hydrocortisone alone had little effect on zoster score. In addition, hydrocortisone cream increased the period of viral shedding and low levels of virus could be detected until day 13 p.i. Similar prolongation of infectious virus in tissues has been shown in previous published (Awan *et al.*, 1998a) and unpublished studies. It is therefore tempting to speculate that the possible extended viral shedding period may cause the late increase in ear thickness seen in mice treated with only hydrocortisone cream or other corticosteroids (data not shown) (Awan *et al.*, 1998a). ME-609 treatment reduced both the amount and length of viral shedding as compared to untreated mice. This is in accordance with previous experiments using combinations of foscarnet and hydrocortisone (Awan *et al.*, 1998a) and combinations of acyclovir and hydrocortisone (unpublished).

In all groups (except the ME-609 group), the experimental variation as measured by the standard error was larger after the peak of infection (day 9-10 p.i.) compared with earlier time points. This could be due to the effectiveness of ME-609 resulting in less scratching of the ears by the mice in this group, presumably due to less itching. As discussed above, mice scratch their ears and this may contribute to the clinical picture at the later stage of infection.

ME-609 was also evaluated in the cutaneous guinea pig model using primary HSV-1 infection. This model is a well-documented primary infection model (Alenius, 1980; Alenius *et al.*, 1982; Alenius & Oberg, 1978) and generalization of results to recurrent infections is, as noted above, problematic. It does, however, confirm the acyclovir efficacy in primary infection and thus indicate sufficient skin penetration of acyclovir from the ME-609 vehicle.

In the cutaneous infection of guinea pigs with HSV-1, treatment with hydrocortisone alone had no effect upon lesion development or duration in comparison with placebo; for example, hydrocortisone cream neither worsened the severity of the lesions nor prolonged their duration. In addition, hydrocortisone cream did not influence viral shedding of the lesions (data not shown). This was expected, as in this model of primary infection the guinea pigs are seronegative for HSV at infection and only develop immunocompetence gradually during the duration of the experiment. As discussed below, the cell culture studies also failed to show stimulation of viral growth by steroids.

ME-609 was more effective in reducing the severity and duration of lesions in the guinea pig model than treatment with acyclovir alone. The beneficial effect of ME-609 was

also seen when treatment was delayed until 48 h p.i.. This was unexpected, given that hydrocortisone alone had no effect and given that this is a primary infection in seronegative animals. One possible explanation is that hydrocortisone has several other effects in addition to the inhibition of inflammation, such as vasoconstriction. The vasoconstrictive effects of hydrocortisone may lead to locally higher concentrations of acyclovir in the skin, resulting in an improved antiviral effect in the guinea pig model. The penetration of acyclovir through the skin has been linked to the antiviral effect as measured in guinea pigs (Freeman *et al.*, 1986; Freeman & Spruance, 1986; Spruance *et al.*, 1986; Spruance *et al.*, 1984). In addition, acyclovir has a problematic penetrational profile when used in a topical formulation and the first commercially available acyclovir formulation, an ointment, has been connected with both poor penetration and poor efficacy in animals and clinical trials (Spruance & Crumpacker, 1982; Spruance *et al.*, 1986; Spruance *et al.*, 1982). An improved acyclovir cream formulation was later developed and this formulation showed better acyclovir penetrational properties as well as improved efficacy (Spruance *et al.*, 1986; Spruance *et al.*, 2002). Acyclovir in the ME-609 formulation penetrates guinea pig skin readily and even better than from the commercially available acyclovir cream as shown in *in vitro* skin penetration experiments described in Figure 4. This result showed that the ME-609 cream formulation delivers acyclovir through intact skin efficiently and is at least as good as the improved acyclovir cream formulation that is available in certain countries.

Glucocorticosteroids have been suggested to potentially stimulate viral growth (and growth of other microorganisms) through two different mechanisms: direct stimulation of viral growth and indirect alteration (inhibition) of the immune system. This concern has primarily been addressed with respect to primary virus infections where the immune system has not previously been exposed to the infectious agent rather than reactivated infections. Results from the primary infection guinea pig model, as well from the ATI mouse model, showed that viral shedding profiles after ME-609 and Zovirax® cream treatment were similar. In addition, the *in vitro* studies of HSV-1-infected cells treated with acyclovir in combination with hydrocortisone showed no change in effect on the viral replication level compared to cells treated with acyclovir alone. In addition, the virus levels of the ME-609-treated animals were below those of the control animal in both animal models. Clearly, the ME-609 concept was safe in both models tested.

Treatment with hydrocortisone alone increased duration of viral shedding in the ATI mouse model representing recurrent infections and measurable virus titres were found 13 days after infection while no virus could be found in the untreated control group beyond day 9. The virus titres in the present study were similar in the untreated and the hydrocortisone cream treated-group at the assessments on days 5 and 7. These results confirmed previous published studies showing that hydrocortisone treatment increased the duration of viral shedding up to day 15 after infection (Awan *et al.*, 1998a). The present study failed to confirm the 100–1000 fold increase in viral titres on days 5 and 7 by hydrocortisone cream treatment previously found (Awan *et al.*, 1998a). The reason for this discrepancy is presently not known. No enhancement of viral growth was however seen in HSV-1-infected cell culture. Nor did treatment with hydrocortisone alone influence the development of lesions in the primary HSV-1 infection model in guinea pigs. This indicates that the enhanced viral growth observed in the ATI mouse model is more likely a result of the altered immune response than direct stimulation of viral replication even though a glucocorticoid response element has been found in the HSV-1 genome (Hardwicke & Schaffer, 1995). Published data on cell culture studies with glucocorticoid treatment of HSV-infected cells are also conflicting. Depending on the cell line used different published studies have shown increases, decreases or no changes in the viral replication level (Hardwicke & Schaffer, 1995; Hardwicke & Schaffer, 1997; Nishiyama & Rapp, 1979; Notter & Docherty, 1978). Clearly more work is needed to resolve this issue.

In conclusion, we have used a novel animal model using a combination of zosteriform infection with adoptive transfer of immunity (ATI) that is believed to better mimic recurrent HSV infections than the currently available models (Awan *et al.*, 1998b). The ATI has previously been shown to increase inflammation (measured by ear thickness) and zoster score with around 50% and to decrease the viral shedding time from 7 to 4 days in parallel to findings in clinical trials (Awan *et al.*, 1998b). In the ATI mouse model, antiviral compounds, such as foscarnet and acyclovir, used alone only show modest beneficial effects, which is reflected in experience from clinical trials. The ME-609 combination of acyclovir and hydrocortisone was more efficacious in reducing the clinical parameters in this animal model. This is probably due to reduction of viral replication, by acyclovir, in combination with modulation of the immune response known to cause the clinical symptom, by hydrocortisone.

The present preclinical studies suggest that ME-609, a new combination of acyclovir and hydrocortisone, may be beneficial in the treatment of recurrent HSV infections in man and thus constitutes a new treatment principle in this disease. The local tolerance of ME-609 was good when tested in animals and in humans. The predicted clinical usefulness of the ME-609 combination principle has been confirmed in two independent recently published clinical trials (Evans *et al.*, 2002; Spruance & McKeough, 2000).

Both studies induced recurrent herpes labialis by exposing individuals to ultraviolet light. Both studies suggested that early treatment with a combination of an antiviral and an immunomodulator decreased the number of patients developing ulcerative HSV lesions by roughly a third compared with treatment with an antiviral alone or placebo. The ulcerative recurrent HSV lesions that did develop, notwithstanding combination treatment, were smaller and healed faster compared with control patients. These clinical data validate the usefulness of the novel ATI mouse model in predicting therapeutic benefit on recurrent HSV disease.

References

Alenius S (1980) Inhibition of herpesvirus multiplication in guinea pig skin by antiviral compounds. *Archives of Virology* 65:149–156.

Alenius S, Berg M, Broberg F, Eklind K, Lindborg B & Oberg B (1982) Therapeutic effects of foscarnet sodium and acyclovir on cutaneous infections due to herpes simplex virus type 1 in guinea pigs. *Journal of Infectious Diseases* 145: 569–573.

Alenius S & Oberg B (1978) Comparison of the therapeutic effects of five antiviral agents on cutaneous herpesvirus infection in guinea pigs. *Archives of Virology* 58:277–288.

Altman D (1991). *Practical Statistics for Medical Research.* Oxford University Press, Oxford.

Aulton ME, Ed. (1988) *Pharmaceutics: the Science of Dosage Form Design.* Churchill Livingstone, London.

Awan A, Harmenberg J, Flink O & Field H (1998a) Combinations of antiviral and anti-inflammatory preparations for the topical treatment of herpes simplex virus assessed using a murine zosteriform infection model. *Antiviral Chemistry & Chemotherapy* 9: 19–24.

Awan AR, Harmenberg J, Kristofferson A & Field HJ (1998b) Herpes simplex virus zosteriform lesions with adoptive transfer of immune cells: a murine model which mimics human recurrent disease. *Antiviral Research* 38:43–53.

Blyth WA, Harbour DA & Hill TJ (1984) Pathogenesis of zosteriform spread of herpes simplex virus in the mouse. *Journal of General Virology* 65:1477–1486.

Corey L, Benedetti JK, Critchlow CW, Remington MR, Winter CA, Fahnlander AL, Smith K, Salter DL, Keeney RE, Davis LG, Hintz MA, Connor JD & Holmes KK (1982a) Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. *American Journal of Medicine* 73:326–334.

Corey L, Nahmias AJ, Guinan ME, Benedetti JK, Critchlow CW & Holmes KK (1982b) A trial of topical acyclovir in genital herpes simplex virus infections. *New England Journal of Medicine* 306: 1313–1319.

Evans TG, Bernstein DI, Raborn GW, Harmenberg J, Kowalski J & Spruance SL (2002) Double-blind, randomized, placebo-controlled study of topical 5% acyclovir-1% hydrocortisone cream (ME-609) for treatment of UV radiation-induced herpes labialis. *Antimicrobial Agents & Chemotherapy* 46:1870–1874.

Field HJ, Bell SE, Elion GB, Nash AA & Wildy P (1979) Effect of acycloguanosine treatment on the acute and latent herpes simplex infection in mice. *Antimicrobial Agents & Chemotherapy* 15: 554–561.

Field HJ, Tewari D, Sutton D & Thackray AM (1995) Comparison of efficacies of famciclovir and valaciclovir against herpes simplex virus type 1 in a murine immunosuppressed model. *Antimicrobial Agents and Chemotherapy* 39:1114–1119.

Freeman DJ, Sheth NV & Spruance SL (1986) Failure of topical acyclovir in ointment to penetrate human skin. *Antimicrobial Agents & Chemotherapy* 29:730–732.

Freeman DJ & Spruance SL (1986) Efficacy of topical treatment for herpes simplex virus infections: predictions from an index of drug characteristics *in vitro*. *Journal of Infectious Diseases* 153:64–70.

Hardwicke MA & Schaffer PA (1995) Cloning and characterization of herpes simplex virus type 1 oriL: comparison of replication and protein-DNA complex formation by oriL and oriS. *Journal of Virology* 69:1377–1388.

Hardwicke MA & Schaffer PA (1997) Differential effects of nerve growth factor and dexamethasone on herpes simplex virus type 1 oriL- and oriS-dependent DNA replication in PC12 cells. *Journal of Virology* 71:3580–3587.

Harmenberg J (1983) Intracellular pools of thymidine reduce the antiviral action of acyclovir. *Intervirology* 20:48–51.

Harmenberg J, Wahren B & Oberg B (1980) Influence of cells and virus multiplicity on the inhibition of herpesviruses with acycloguanosine. *Intervirology* 14: 239-44.

Hill TJ, Field HJ & Blyth WA (1975) Acute and recurrent infection with herpes simplex virus in the mouse: a model for studying latency and recurrent disease. *Journal of General Virology* 28: 341–353.

Hubler WR Jr, Felber TD, Troll D & Jarratt M (1974) Guinea pig model for cutaneous herpes simplex virus infection. *Journal of Investigative Dermatology* 62:92–95.

McKeough MB & Spruance SL (2001) Comparison of new topical treatments for herpes labialis: efficacy of penciclovir cream, acyclovir cream, and n-docosanol cream against experimental cutaneous herpes simplex virus type 1 infection. *Archives of Dermatology* 137:1153–1158.

Nagafuchi S, Oda H, Mori R & Taniguchi T (1979) Mechanism of acquired resistance to herpes simplex virus infections as studied in nude mice. *Journal of General Virology* 44:715–723.

Nishiyama Y & Rapp F (1979) Regulation of persistent infection with herpes simplex virus *in vitro* by hydrocortisone. *Journal of Virology* 31:841–844.

Notter MF & Docherty JJ (1978) Steroid hormone alteration of herpes simplex virus type 1 replication. *Journal of Medical Virology* 2: 247–252.

Poli G, Dall'Ara P, Binda S, Santus G, Poli A, Cocilovo A & Ponti W (2001) Value of the dorsal cutaneous guinea pig model in selecting topical antiviral formulations for the treatment of recurrent herpes simplex type 1 disease. *Arzneimittelforschung* 51: 433–438.

Raborn GW, Martel AY, Lassonde M, Lewis MA, Boon R & Spruance SL (2002) Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *Journal of the American Dental Association* 133:303–309.

Reichman RC, Badger GJ, Guinan ME, Nahmias AJ, Keeney RE, Davis LG, Ashikaga T & Dolin R (1983) Topically administered acyclovir in the treatment of recurrent herpes simplex genitalis: a controlled trial. *Journal of Infectious Diseases* 147:336–340.

Richards DM, Carmine AA, Brogden RN, Heel RC, Speight TM & Avery GS (1983) Acyclovir. A review of its pharmacodynamic properties and therapeutic efficacy. *Drugs* 26:378–438.

Spruance SL (1992) The natural history of recurrent oral-facial herpes simplex virus infection. *Seminars in Dermatology* 11:200–206.

Spruance SL & Crumpacker CS (1982) Topical 5 percent acyclovir in polyethylene glycol for herpes simplex labialis. Antiviral effect without clinical benefit. *American Journal of Medicine* 73:315–319.

Spruance SL, Freeman DJ & Sheth NV (1986) Comparison of foscarnet cream, acyclovir cream, and acyclovir ointment in the topical treatment of experimental cutaneous herpes simplex virus type 1 infection. *Antimicrobial Agents & Chemotherapy* 30:196–198.

Spruance SL & McKeough MB (2000) Combination treatment with famciclovir and a topical corticosteroid gel versus famciclovir alone for experimental ultraviolet radiation-induced herpes simplex labialis: a pilot study. *Journal of Infectious Diseases* 181:1906–1910.

Spruance SL, McKeough MB & Cardinal JR (1984) Penetration of guinea pig skin by acyclovir in different vehicles and correlation with the efficacy of topical therapy of experimental cutaneous herpes simplex virus infection. *Antimicrobial Agents & Chemotherapy* 25:10–15.

Spruance SL, Nett R, Marbury T, Wolff R, Johnson J & Spaulding T (2002) Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrobial Agents & Chemotherapy* 46: 2238–2243.

Spruance SL, Overall JC, Jr., Kern ER, Krueger GG, Pliam V & Miller W (1977) The natural history of recurrent herpes simplex labialis: implications for antiviral therapy. *New England Journal of Medicine* 297:69-75.

Spruance SL, Rea TL, Thoming C, Tucker R, Saltzman R & Boon R (1997) Penciclovir cream for the treatment of herpes simplex labialis. A randomized, multicenter, double-blind, placebo-controlled trial. Topical Penciclovir Collaborative Study Group. *Journal of the American Medical Association* 277:1374–1379.

Spruance SL, Schnipper LE, Overall JC, Jr., Kern ER, Wester B, Modlin J, Wenerstrom G, Burton C, Arndt KA, Chiu GL & Crumpacker CS (1982) Treatment of herpes simplex labialis with topical acyclovir in polyethylene glycol. *Journal of Infectious Diseases* 146:85–90.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

EXHIBIT 10

Food and Drug Administration
Rockville MD 20857

IND 58,500

Inveresk Research (North America) Inc
Attention: David J. Dempsey
Director, Regulatory Affairs
4470 Redwood Hwy Ste 101
San Rafael, CA 94903

JUL 9

JUL 15 1999

INVERESK RESEARCH

Dear Mr. Dempsey:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 58,500

Sponsor: Medivir AB

Name of Drug: ME-609 Cream (Acyclovir 5%/Hydorcortisone 1%)

Date of Submission: June 18, 1999

Date of Receipt: June 21, 1999

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information (21 CFR 312.32(c)(2)); (2) reporting any adverse experience with use of the drug that is both serious and unexpected in writing no later than 15 calendar days of initial receipt of the information (21 CFR 312.32(c)(1)); and (3) submitting annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in quadruplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Viral Drug Products, HFD-530
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this submission, please contact Melissa Truffa, R.Ph., at (301) 827-2335.

Sincerely,

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Regulatory correspondence log

EXHIBIT 11

Project: ME-609
Country: USA
IND 58,500

Date	Serial #	To	Description
1998-11-18_	N/A	DAVDP	Pre-IND submission notification
1998-11-24	N/A	DAVDP	Pre-IND documentation submission
1999-04-15	N/A	Medivir	FDA comments to pre-IND documentation
1999-06-18	000	DAVDP	Initial IND application and response to pre-IND comments
1999-07-09	N/A	Inveresk (US agent)	FDA acknowledgement of IND, assignment of IND # 58,500
1999-07-21	N/A	Inveresk	FDA fax. Clearance to proceed with clinical trial 98-609-003. Comments to inital IND application (clinical and CMC).
1999-08-06	001	DAVDP	Information amendment: Chemistry. Certificates of analysis for clinical supply batches.
1999-08-24	N/A	Inveresk	FDA letter. Same content as 21 July fax.
1999-09-17	N/A	Inveresk	FDA fax. Comments on Laser Doppler Velocimetry.
1999-11-16	002	DAVDP	Response to FDA request for information, addressing comments of July 21, Aug 24, Sep 17, 1999.
2000-04-06	003	DAVDP	Information amendment: Chemistry. Stability data for clinical supply batches
2000-04-29	004	DAVDP	Protocol amendment for clinical trial 98-609-003. Amendment 2 (dated April 13, 2000) to increase patient population.
2000-07-11	005	DAVDP	Information amendment: Chemistry. Modification in manufacturing process. Certificates of analysis for new clinical supply batches.
2000-07-13	006	DAVDP	Protocol amendment for clinical trial 98-609-003. Amendment 2 (revised June 22, 2000) to increase patient population.
2000-09-18	007	DAVDP	Response to FDA request for information. Additional responses to comments of July 21, Aug 24, Sep 17, 1999.
2000-09-20	008	DAVDP	Annual report. July 21, 1999 to July 20, 2000.
2001-08-17	009	DAVDP	General correspondence: Omnicare Clinical Research is new US agent
2001-08-21	009	DAVDP	Transfer of obligation. Letter from Omnicare.
2001-09-07	010	DAVDP	Information amendment, CMC. Hydrocortisone source both France and Kalamazoo
2001-09-12	011	DAVDP	Annual Report. July 21, 2000 to July 20, 2001
2002-09-16	012	DAVDP	Annual Report. July 21, 2001 to July 20, 2002
2003-09-04	013	DAVDP	Annual Report. July 21, 2002 to July 20, 2003
2004-02-13	014	DAVDP	Mary Holland is new US agent (fax + letter)
2004-02-16	015	DAVDP	Request for EOP2 meeting
2004-02-25	-	DAVDP	Phone call about current FDA project manager.

Date	Serial #	To	Description
2004-02-25	-	Medivir	Email. Address for desk copies.
2004-02-27	-	Medivir	Email. Questions about study reports to be submitted
2004-02-27	-	DAVDP	Email response to above questions.
2004-03-04	-	DAVDP	Phone call. Tentative information on EOP2 meeting date.
2004-03-05	016	DAVDP	Submission of non-clinical and clinical reports.
2004-03-08	-	Medivir	Phone call about status of report submission and request for fax with synopses and table of contents of clinical reports.
2004-03-08	-	DAVDP	Email about arrival of report submission.
2004-03-09	-	Medivir	Phone call. Confirmation on EOP2 meeting April 21
2004-03-09	-	Medivir	Written confirmation of EOP2 meeting on April 21.
2004-03-18	017	DAVDP	Briefing package for EOP2 meeting
2004-03-18	-	DAVDP	Seven desk copies of above package
2004-03-22	-	Medivir	Email confirming receipt of package and requesting electronic version of section 1.3
2004-03-25	-	DAVDP	Email submission of electronic version of section 1.3
2004-04-16	-	DAVDP	Email. Information about coming CMC updates and brief CMC section overview.
2004-04-16	-	Medivir	Email confirmation of receipt of CMC email.
2004-04-20	-	Medivir	Fax regarding April 21 meeting. Reclassification of meeting and main issues for discussion.
2004-04-30	-	DAVDP	Email submission of Medivir's meeting minutes
2004-05-17	-	Medivir	FDA record of April 21 meeting
2004-05-19	-	Medivir	Microbiology comments.
2004-09-08	018	DAVDP	Clinical development information package: Discussion of comparator arms
2004-09-18	019	DAVDP	Annual Report. July 21, 2003 to July 20, 2004.
2004-11-03		Medivir	Clinical comments to Sept 8 submission
2004-11-19	-	Medivir	Email response regarding internal discussions on jurisdiction of IND
2004-11-29	020	DAVDP	Request for telecon to discuss jurisdiction of IND
2004-12-08	-	DAVDP	Email correction of serial number for Nov 29 submission
2004-12-09	-	DAVDP	Email: Confirmation of information regarding decision that DAVDP will continue as lead division
2004-12-13	-	DAVDP	Email: Objectives for Dec 15 telecon
2004-12-15	-	-	Medivir internal meeting minutes from Dec 15 telecon
2005-01-28	021	DAVDP	Clinical development information package Request for telecon on clinical development plan
2005-02-11	-	Medivir	Scheduling of telecon for March 21
2005-02-18	-	DAVDP	Extra copies of clin dev information package
2005-03-11	-	J. Jenkins, Office of New Drugs	Request for designation of the lead review division
2005-03-18	-	Medivir	Clinical comments to SN 021, for March 23 meeting
2005-03-28	-	Medivir	Clinical comments (one single study)

Date	Serial #	To	Description
2005-04-04	-	DAVDP	Email with questions on content of March 28 memo
2005-04-08	-	DAVDP	Medivir summary of March 23 meeting
2005-04-15	023*	DAVDP	Major CMC amendment
**Serial #022 was inadvertently not used*			
2005-04-20	-	Medivir	FDA Record of March 23 meeting
2005-04-27	-	Medivir	Clinical statistical comments referring to April 26 telecon
2005-04-29	024	DAVDP	Medivir summary of April 26 telecon and response to FDA comments of April 27
2005-05-04	025	DAVDP	Request for End of Phase 2 Meeting
2005-05-04	026	DAVDP	Proposal for acyclovir susceptibility testing and safety study in immunocompromised
2005-05-10	-	Medivir	Clinical/statistical comments to Medivir April 29 submission (#024)
2005-05-13	027	DAVDP	Medivir summary of May 11 telecon
2005-05-18	-	Medivir	Confirmation of EOP2 meeting on July 6
2005-05-19	028	DAVDP	Phase 3 study synopsis and sample size calculations
2005-05-19	029	DAVDP	Supplementary reports (stability, in vitro release and mouse efficacy) that should have been in the April 15 submission (#023)
2005-06-02	-	Medivir	Chemistry comments to Medivir April 15 submission (#023)
2005-06-03	030	DAVDP	Clinical study report for dermal irritation study
2005-06-03	031	DAVDP	Briefing package for EOP2 meeting July 6
2005-06-03	-	DAVDP	Desk copies for submissions #026, 028, 030 and 031
2005-06-30	-	Medivir	Draft comments for July 6, 2005 meeting
2005-07-01	-	DAVDP	Email clarification on formulation and dermal safety
2005-07-01		Medivir	Comment on dermal irritation study
2005-07-08	-	Medivir	Comment on photosafety study requirements
2005-07-14	032	DAVDP	Medivir minutes from July 6 EOP2 meeting
2005-08-08	-	Medivir	Official minutes from July 6 EOP2 meeting
2005-09-15	033	DAVDP	Annual report for July 21, 2004 to July 20, 2005
2005-10-01	034	DAVDP	Response to comments regarding photosafety testing and dermal irritation study
2005-10-28	035	DAVDP	Draft Patient Diary Card (for pivotal phase 3 study) submitted for comments
2005-11-09	-	Medivir	DDDP comments on photosafety response (SN#034)
2005-12-05	036	DAVDP	Response to chemistry comments June 2, 2005
2005-12-22	037	DAVDP	Request for Special Protocol Assessment for clinical protocol 609-04
2006-01-13	038	DAVDP	Clinical protocol 609-06 (immunocompromised subjects) for comments
2006-01-13	039	DAVDP	Request for wider pH limits in drug product specification
2006-01-13	040	DAVDP	Final study report for dermal sensitization study (study no 604603)

Date	Serial #	To	Description
2006-01-13	-	Medivir	Acknowledgement of receipt of Special Protocol Assessement (SN#037, submitted Dec 22, 2005, received Dec 29, 2005
2006-01-26	-	Medivir	Chemistry comments to response submitted Dec 5, 2005 (SN#036)
2006-02-10	-	Medivir	Special Procotol Assessment - comments
2006-02-27	041	DAVDP	Pediatric Use Study (request for waiver for study in younger children) and request for Type A meeting
2006-03-02	-	Medivir	Chemistry comments to SN#037 – approval of wider pH limits
2006-03-07	-	Medivir	Clinical comments to SN#038 – study in immunocompromised subjects
2006-03-14	-	Medivir	Microbiology comments to SN#038 – study in immunocompromised subjects
2006-03-15	-	Medivir	Clinical comments to SN#040 (dermal sensitization study report) – comments on clinical development from DDDP
2006-03-16	-	Medivir	Schedule of telecon on May 11, 2006 to discuss request for waiver from pediatric studies in younger children (SN#041)
2006-03-17	042	DAVDP	Response to comments on protocol 609-04 (SPA) dated Feb 10, 2006.
2006-03-29	043	DAVDP	CMC information (acyclovir cream, vehicle cream, viscosity validation, stability protocol)
2006-04-06	044	DAVDP	Response to DDDP's clinical comments dated March 15, 2006
2006-04-06	045	DAVDP	Response to clinical and microbiology comments to protocol 609-06 (IC) dated March 7 and March 14, 2006.
2006-04-18	-	Medivir	Email response regarding patient diary card submitted October 28, 2005
2006-04-28	-	Medivir	Statistics comments to SN#042 - plan for reassessment of sample size
2006-05-05	046	DAVDP	Final protocol study 609-04 + transfer of obligations + updated IB
2006-05-09	-	Medivir	Clinical comments to SN#041 – pediatric studies
2006-05-16	-	Medivir	FDA minutes from May 11 telecon re pediatric studies
2006-05-17	-	Medivir	Microbiological comments to SN#045 – IC study 609-06
2006-05-19	047	DAVDP	Minutes from May 11 telecon and synopsis for study 609-07 (adolescent study)
2006-06-01	048	DAVDP	Revised plan for reassessment of sample size and minutes from May 2 telecon
2006-06-29	049	DAVDP	Response to clinical comments dated Nov 9, 2005 regarding photosafety studies
2006-06-29	050	DAVDP	Response to microbiology comments dated May 17, 2006 regarding clinical protocol 609-06 (IC)

Date	Serial #	To	Description
2006-06-29	051	DAVDP	Protocol amendment no. 1 + new investigator Study 609-04
2006-07-21	052	DAVDP	New investigators Study 609-04
2006-08-08	-	Medivir	DDDP clinical comments to SN#049 – photosafety
2006-08-18	053	DAVDP	Protocol amendment no. 2 + new investigators Study 609-04
2006-08-25	-	Medivir	Clinical comments to SN#048 - reassessment of sample size in study 609-04. Microbiology comments to SN#050 - PCR testing in study 609-06.
2006-09-18	054	DAVDP	Annual report 7/21/2005 – 7/20/2006
2006-09-18	055	DAVDP	New investigators Study 609-04
2006-09-18	056	DAVDP	Response to clinical comments dated August 8, 2006 – commitment to perform photosafety studies
2006-09-20	-	Medivir	Emailing request for track-changes version of protocol in submission #053
2006-09-29	057	DAVDP	Response to microbiology comments dated August 25, 2006 – PCR testing in study 609-06
2006-09-29	058	DAVDP	Response to clinical comments dated August 25, 2006 – reassessment of sample size in study 609-04
2006-09-29	059	DAVDP	Resubmission of Study 609-04 Protocol Amendment #2: Change in Protocol
2006-10-25	060	DAVDP	New Investigators for Study 609-04
2006-12-04	061	DAVDP	New Investigators for Study 609-04
2006-12-26	062	DAVDP	New Investigators for Study 609-04
2007-02-13	063	DAVDP	Clinical protocols KGL#6201 (phototoxicity) and KGL#6202 (photocontact allergenicity) for comments
2007-02-23	064	DAVDP	Response to Microbiology Comments related to Protocol 609-06 (IC)
2007-03-09		Medivir	Clinical comments from DDDP to SN#63 (phototoxicity and photocontact allergenicity)
2007-03-12	065	DAVDP	SAP for Study 609-04
2007-03-14	066	DAVDP	Final Clinical protocols KGL#6201 (phototoxicity) and KGL#6202 (photocontact allergenicity) + investigator information
2007-04-04		Medivir	Response to SN#064 on d-thymidine proposal
2007-04-14	067	DAVDP	Response to Microbiology Comments related to Protocol 609-06 (IC) on d-thymidine proposal
2007-04-23	068	DAVDP	Protocol Amendment No. 3. Study 609-04
2007-05-01		Medivir	Statistical comments to SN#065 on SAP
2007-06-12	069	DAVDP	Protocol Amendment No. 4. Study 609-04
2007-06-12	070	DAVDP	Revised SAP (Version 3.1) for study 609-04 and response to FDA comments from May 1
2007-06-21		Medivir	Response to SN#064 on d-thymidine proposal
2007-07-24		Medivir	Statistical comments to SN#070 on revised SAP
2007-08-01	071	DAVDP	New Investigators for Study 609-04
2007-08-08	072	DAVDP	New Investigator for Study 609-04

Date	Serial #	To	Description
2007-09-07	073	DAVDP	Pre-NDA Meeting Request General/Nonclinical/Clinical
2007-09-10	074	DAVDP	Pre-NDA Meeting Request CMC
2007-09-14	-	Medivir	CMC meeting granted by FDA
2007-09-19	075	DAVDP	Annual Report for period 21/7-2006 to 20/7-2007
2007-09-21	-	Medivir	General/nonclinical/clinical meeting granted by FDA
2007-09-25	076	DAVDP	Study KGL6020 – Protocol Amendment 1: Challenge phase with individual ingredients
2007-10-03	077	DAVDP	Protocol Amendment No. 5. Study 609-04
2007-10-10	078	DAVDP	CMC Pre-NDA Meeting Package
2007-10-12	079	DAVDP	General/Nonclinical/Clinical Pre-NDA Meeting Package
2007-10-30	080	DAVDP	New Investigator Study 609-04
2007-11-07		Medivir	FDA comments on SN#079 Pre-NDA meeting package
2007-11-08		Medivir	FDA comments on SN#078 CMC Pre-NDA meeting package
2007-11-09		Medivir	FDA comments on SN#076 Study KGL6202
2007-12-04	081	DAVDP	Response to Clinical Comments - Clinical Study Protocol KGL #6202, Amendment 1
2007-12-13		Medivir	FDA official minutes from CMC Pre-NDA meeting
2007-12-20	082	DAVDP	Response to statistical comments. SAP version 3.2
2007-12-21	083	DAVDP	CMC pre-NDA Meeting – Sponsor meeting minutes
2008-02-13		Medivir	ROC with FDA office of Generics re. Inactive Ingredients Limits (Poloxamer 188; Isopropyl Myristate)
2008-02-14	084	DAVDP	CMC: in vitro release data and homogeneity data for evaluation
2008-03-06	085	DAVDP	Pre-NDA Meeting Request General/Nonclinical/Clinical
2008-04-23	086	DAVDP	Pre-NDA Meeting Briefing Package
2008-03-27		Medivir	General/nonclinical/clinical meeting granted by FDA on May 22
2008-05-05		Medivir	FDA clinical comments to SN#085, request for further information
2008-05-09	087	DAVDP	Response to FDA clinical comments from May 5
2008-05-15		Medivir	FDA contact re Pre-NDA meeting (e-mail)
2008-05-19		Medivir	FDA Pre-NDA meeting responses
2008-05-21	088	DAVDP	Response to FDA Request: Correction to pre-NDA Meeting Briefing Package
2008-06-03	089	DAVDP	Response to FDA request for Information on study sites on study 609-04
2008-06-12	090	DAVDP/ DDDP	Teleconference request and briefing package (Citric acid content)
2008-06-13	091	DAVDP	Sponsor Pre-NDA meeting minutes
2008-06-17		Medivir	FDA response to SN#084, homogeneity data
2008-06-24		Medivir	FDA official Meeting minutes Pre-NDA meeting

Date	Serial #	To	Description
2008-06-25	092	DAVDP	Response to FDA comments
2008-06-30		Medivir	FDA response to SN#90, cancellation of teleconference
2008-07-11	093	DAVDP	Request for clarification/Revision to FDA issued pre-NDA Meeting Minutes
2008-07-11		FDA	Request for Small Business Waiver of the New Drug Application Fee
2008-07-30	094	DAVDP	Request for Review of Sample SAS Transport File Format
2008-08-11	095	DAVDP	CMC information amendment: Appearance Specification and Microscopic Method
2008-08-28		Medivir	SAS file comments
2008-09-16	096	DAVDP	Annual Report July 2007-July 2008

NDA Regulatory correspondence log

Project: ME-609
Country: USA
NDA 22-436

Date	Serial #	To	Description
2008-09-29	0000	DAVDP	505(b)2 NDA submission
2008-10-27	mail	DAVDP	Clarification of location of clinical data
2008-10-28	0001	DAVDP	Request for Trade name review
2008-10-30	0002	DAVDP	Addendum study 609-06: 12 month follow-up data
2008-11-07	mail	Medivir	Request from Division of Scientific Investigations (DSI)
2008-11-14		DSI	Study 609-04: Site specific information
2008-11-19	0003	DAVDP	Updated User Fee Cover Sheet
2008-12-05	0004	DAVDP	Updated form FDA 356h
2008-12-15		DSI	Site specific CRFs for 609-04
2008-12-23	0005	DAVDP	Response to filing communication
2009-01-08	Fax	Medivir	ROC 07: Letter re. Small Business waiver
2009-03-19	Fax	Medivir	ROC 08: Clinical comments re inspection of site 17
2009-03-19	Fax	Medivir	ROC 09: Clinical Pharmacology Comments
2009-04-03	Fax	Medivir	ROC 10: Submit draft ped. Study synopsis. Comments on studies 604598 and 604603
2009-04-16	0006	DAVDP	Response to clinical comments and comments from DDDP
2009-04- 17	Mail	Medivir	ROC 11: regarding submission 0006 (mail)
2009-04-17	0007	DAVDP	Response to clinical site investigation comments (March 19)
2009-04-20	0008	DAVDP	Paediatric plan
2009-04-21		Medivir	ROC 12: FDA wants more specific date for Paed study
2009-04-23		Medivir	ROC13: Statistics comments on ME-609-06
2009-04-23	0009	DAVDP	Updated paediatric study plan
2009-04-30	0010	DAVDP	Response to Clinical Pharmacology Questions (March 19)
2009-05-04		Medivir	ROC 14: Proposed tradename unacceptable
2009-05-07	Fax	Medivir	ROC 15: Annual user fees (no fees are due)
2009-05-08	0011	DAVDP	Response to Statistics Comments (April 23)
2009-06-03	0012	DAVDP	Final Clinical Study Report 609-06
2009-06-03		Medivir	ROC 16: trade name review
2009-06-10		Medivir	ROC 17: Label and Tube Example
2009-06-16		Medivir	ROC 18: Clarification from David Araojo
2009-06-24		Medivir	ROC 19: Additional Label revisions from DDDP
2009-06-29	0013	DAVDP	Response to labeling Comments/Revisions
2009-07-02		Medivir	ROC 20: Label comments microbiology
2009-07-02		Medivir	ROC 21: Attachment
2009-07-15	0014	DAVDP	Response to Labeling Comments (Microbiology – 02 July 2009)
2009-07-20		Medivir	ROC 23: CMC Comments

Date	Serial #	To	Description
2009-07-23		Medivir	ROC 24: Chemistry comments
2009-07-27		Medivir	ROC 25: Label revision
2009-07-27	0015	DAVDP	Response to Information request letter (20 July 2009) and Request for Labeling Revisions (27 July 2009)
2009-07-31		Medivir	FDA APPROVAL LETTER

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,337,324
DATED : January 8, 2002
INVENTOR(S) : Harmenberg et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16,
Line 16, delete "claim 31" and substitute therefor -- claim 32 --.

Signed and Sealed this

Fourteenth Day of May, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

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Patent Bibliographic Data					09/25/2009 06:32 PM
Patent Number:	6337324		**Application Number:**	08612847	
Issue Date:	01/08/2002		**Filing Date:**	03/08/1996	
Title:	NOVEL PHARMACEUTICAL COMBINATION				
Status:	This patent has been reissued as: RE39264			**Entity:**	Large
Window Opens:	01/08/2013	**Surcharge Date:**	07/09/2013	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	06/17/2005 06/09/2005	Payor Number Assigned. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
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According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

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PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,337,324	$900.00	$0.00	06/09/05	08/612,847	01/08/02	03/08/96	04	NO	11003326-202

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Atty Docket No.: 1718-0214P

Inventor: Johan G. HARMENBERG et al.

Patent No.: RE39,264 E **Issue Date:** September 5, 2006
Title: PHARMACEUTICAL COMBINATION

Documents Filed (3 copies of each):

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Corrected Request for Patent Term Extension (16 pages)

Transmittal Form (1 page)

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Fee Transmittal (1 page)

Exhibit 1 (12 pages) ; Exhibit 2 (2 pages)

Exhibit 3 (2 pages); Exhibit 4 (13 pages)

Exhibit 5 (18 pages); Exhibit 6 (14 pages)

Exhibit 7 (2 pages); Exhibit 8 (2 pages)

Exhibit 9 (11 pages); Exhibit 10 (2 pages)

Exhibit 11 (9 pages); Exhibit 12 (1 page)

Exhibit 13 (2 pages)

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Sender's Initials: LRS/SWG/awl **Date:** September 28, 2009

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Exhibit 5 (18 pages); Exhibit 6 (14 pages)
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Exhibit 11 (9 pages); Exhibit 12 (1 page)
Exhibit 13 (2 pages)